American Journal of Obstetrics and Gynecology

VOL. 28 ST. LOUIS, NOVEMBER, 1934 No. 5

American Gynecological Society

Fifty-Ninth Annual Meeting

THE LICENSE TO PRACTICE MEDICINE

PRESIDENT'S ADDRESS

FRANK W. LYNCH, M.D., SAN FRANCISCO, CALIF.

FIFTY-NINE years ago a small group of men met in New York to found this, the first national organization in the world devoted to the study of obstetrics and gynecology. Time has dealt kindly with our Society; as the years have passed, enshrined upon our rolls have been the names of nearly all who have achieved fame in our specialty. To be a Fellow and to follow in the footsteps of my beloved Chief was my fondest desire. To be your president is an undreamed-of honor, for which there are no words with which I may express my gratitude to you for this unexpected evidence of kindness and esteem.

Since our last meeting, Death has passed our active Fellowship by, but has claimed one Honorary Fellow. August Martin, a guest of the Society in 1887 and an Honorary Fellow since 1888, died in Berlin at the ripe age of eighty-seven. Distinguished son of a distinguished father, and known through the world as an able investigator, teacher, surgeon, author, editor and founder of a great medical journal, he was the first clinician, a full generation in advance of his time, who recognized the need of properly peritonizing the raw surfaces after an abdominal operation. The Society has been honored by his Fellowship.

We have been fortunate in these troubled days when the whole world seemed going upside down that our Society had no major problems with which it must contend. Our membership has remained thor-

The articles contained in this issue are papers read at the Fifty-Fifth Annual Meeting of the American Gynecological Society held at White Springs, West Virginia, May 21, to 23, 1934.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

oughly representative, prominent, and vitally interested in the affairs of the medical world. There are some, however, who think the Society is too small.

At the first meeting of the Society, the proper size of the membership was a matter of serious consideration and debate. In discussing the policies of the new Society, our first president, the distinguished Fordyce Barker, impressed the Fellows with the fact that "the status of this Society in the scientific world will be determined by the character and value of the papers published in its *Transactions* and by the tone and ability of its discussions." For which reason he urged that the right to Fellowship should be restricted to those who had won a conceded personal and professional eminence and not to those who give promise as to the future, "as they can afford to wait until time has demonstrated that the buds and blossoms of youth have developed the fruit which ripens in an established reputation with the profession at large. Honors cheapened by being made common are but slightly esteemed."

The question of expansion has come before this body for discussion many times in the last fifty years; the arguments for and against such action have always been the same. And, on each occasion, our Fellows have confirmed the feeling of our founders and the membership list has remained small.

From the very beginning, the Society has been composed of investigators, practitioners, or teachers, who represented rather completely the gynecologic-obstetric staffs of the leading medical schools and hospitals of this country and Canada. Started with a limit of sixty, the permissible active Fellowships were increased to one hundred in 1880 under the presidency of J. Marion Sims, at which number it still remains. Yet, in all these years, the membership has rarely been completely filled; those entrusted with the guidance of the Society believing that one or two vacancies was a wise precaution. Nor, in all this time, has it ever been necessary to refuse admission to an unusually worthy candidate because the Fellowship was already full. Nor, on the contrary, have large delegations been the rule, our ranks filling with the younger generations in a small and even stream. It might be very easy to change the complexion of a happy Society by the admission of too many new Fellows at any one time. And, under this plan, originated by our founders, the Society has prospered for these many years.

For twelve years, ours was the only national organization of obstetricians and gynecologists to which one interested in these subjects might belong. For this reason, therefore, the size of the Society was first increased. Now, there are several gynecologic and obstetric organizations which draw their memberships from many states. So the original reason for expansion no longer obtains. Moreover, as time

goes on, every society develops its own characteristics as clearly marked as those of a man. These many years, we have attracted teachers and investigators, men of the widest renown. I warmly favor the retention of our past policies, and the continuation of a small membership selected for achievement, ability, and personality.

* * * * *

The recent passing of Richardson, the last of our founders, and now that of our great German Honorary Fellow serves to remind us how close we are to the Dark Ages of Medicine and of the great advances that have been made in the lifetime of these two men. The development of medicine has been a favorite theme for discussion from this rostrum by many who have preceded me in this chair. The evolution of our specialists has been traced so completely in our *Transactions* that it would be futile to attempt to add more. I propose, therefore, with your permission to speak on a subject nearly as old as either of these—one which was the chief reason for the organization of the American Medical Association, but which seemed settled when the long fight against the proprietary medical schools was finally won. But the passage of time brings changes and new conditions, and discussion of the license to practice medicine has come up anew. Forty-five years ago, in the fight against the proprietary schools, Osler said, "It makes one's blood boil to think that there are sent out year by year, scores of men called doctors, who have never attended a case of labor, and who are utterly ignorant of the ordinary everyday diseases which they may be called upon to treat; men who may never have seen the inside of a hospital ward." How true that sounded, even in recent years. Twenty-five years ago the American College of Surgeons under our own Franklin Martin started its fight to improve American surgery and hospital conditions. The formation of the National Board of Medical Examiners, in an attempt to raise and equalize the minimal qualifications of our practitioners, was the second marked protest against the present system of licensure. This has been followed by a widespread movement throughout the country to ensure that those posing as specialists are properly qualified as such. Eight certification boards are now functioning in this country, or are in the process of formation.

The whole question of certification of a specialist has aroused so great interest that the American Medical Association has been drawn into the fray. Yet, while the solution of this question will come very shortly, the basic question of proper qualifications for practice in general remains untouched.

* * * * *

Medicine was developing almost by leaps and bounds when the Society was founded, but it was not because of the system of medical

education that we had employed, as Keene so ably has shown. Rather was it due to those leaders in medicine who from time immemorial have developed by sheer native ability alone and who achieved the impossible in spite of unfavorable medical conditions which surrounded them. These are they who started the earlier medical schools and trained others to carry their work along. Yet their successors rarely were men of equal ability, for genius is born and seldom made. In such a list are Paré, Mauriceau, Sydenham, Smellie, the Hunters, Louis, and many other great Europeans who did so much to make possible medicine of our time. In this country there was McDowell, the dreamer, but a man of most stern reality withal; Nathan Smith who founded many medical schools of his period and whose teachings are embodied in parts of discussions of present-day medical and surgical problems and who appears greater year by year; and Marion Sims who, with McDowell, opened to the world the possibility of modern gynecology and surgery. They, together with nearly all of our founders, had received only sparks from their teachers or preceptors to light their medical way. Some few of our founders owed some of their inspiration to association with great European clinicians in their younger and most impressionable years. One of these was Chadwick who, more than any other man, was responsible for founding this Society.

Our founders were developments of the proprietary schools of medicine against whose methods of instruction the American Medical Association had fought ineffectually for so long. Yet, in spite of the achievements of these leaders, the rank and file of our profession were poorly trained. The factors which are responsible for the high medical education of the average physician in America at present were undeveloped in that age. The medical schools of that period, with few exceptions, were hopeless from the modern point of view. They gave neither training nor inspiration to the average student who was turned out to flounder along in practice as best he could. Yet the school gave him the right to practice medicine by merely registering his degree. In the early days of the Society medical books were few and costly, as were medical magazines, and there were few medical societies in which those interested in special fields of medicine could meet and exchange their views. The rank and file of the profession seldom attempted abdominal operations in our founders' day without much conference and preparation, very probably because the mortality of such procedures was tremendous—at least 75 per cent on the average as late as 1873. At that time, however, our founder, Atlee, had removed 264 ovarian tumors with 70 per cent recoveries, indicating that better results attend the better trained man. The restrictions of surgery to the exceptional case made the right to practice medicine less important than now.

American medical schools of the present far surpass the dream of the most sanguine of our founders in providing the student with a basic training for the intelligent practice of our profession. The whole science and art of medicine is now presented in a logical sequence which demands that every subject having an influence on the interpretation of another shall have precedence in a curriculum prescribed by state laws. No longer is the approach to clinical work through anatomy alone, as in the older days, but through three and a half years of science in the premedical and preclinical courses. The student comes early in contact with the sick patient, both in the hospitals and dispensaries, and receives much individual instruction. As a result, with three years of premedical work and four years in the medical school, he has seven years of medicine before his graduation. The medical schools are banded together through the Association of American Medical Colleges and Councils of Education of the American Medical Association in an amalgamation at least as strong as in the proprietary school days. But now no longer is the object of the union to combat every movement to raise the standards of medical education, as in our founders' day, but to find ways and means of improving the curriculum and methods of instruction so that the student, when graduated, shall have been trained in every reasonable way.

The world, however, is learning that a finished physician cannot be made by medical school courses alone. Even with two and a half years devoted to clinical instruction, there is not time to present all subjects in a complete way. With the rapid development of clinical medicine, new subjects constantly demand consideration in the curriculum. The best that a medical school can hope to do under present conditions is to teach the fundamentals and salient features of disease clearly and convincingly. It cannot hope to turn out all students proficient in the use of modern complicated diagnostic instruments of precision, or in unusual laboratory methods, or in the mechanical technic of surgery; to do this would add years to a curriculum and be an economic waste for students graduating too late in life as it is. Many students may not need to know more than their uses; those who wish actually to use them should learn how after graduation.

General practice is built around obstetrics, gynecology, and surgery, none of which can be taught completely in the present type of medical school curriculum. The theory and its related science can be developed as fully as needs be, but the handicraft of the subjects can be learned only after graduation.

A few years ago obstetrics was slighted in the curriculum, but the high death rate in childbed in the United States aroused public interest and was responsible for many much-needed improvements in the method of teaching. As a result, obstetrics is now taught as well in the better medical schools as is possible with the present system. The

poorer schools, however, still teach this subject in a hopeless manner. As a matter of fact, the opinion is growing that the difference between the best and the worst of the medical schools at present is about as much as it was in the days of the proprietary schools.

All graduates of the leading schools have had sufficient experience to undertake minor surgery and have attended enough patients in the prenatal clinic and delivery room to warrant their care of a normal obstetric case. Some schools drill their students in the details of operations that may cure certain acute life-threatening surgical conditions, and teach them operative technic by permitting them to do the surgical work necessary in any animal experimentation. All schools train their pupils on the obstetric mannikin, so that they may attempt delivery in blocked labor if there is no other aid in sight. The schools properly give more technical drill in obstetrics than in surgery, since it is more difficult to obtain adequate training in the former field during subsequent hospital years. Yet the most that any medical school can do in either subject is to give the student a very small training in the handicraft which is essential to the general practice of medicine. A medical school, as constituted at present, cannot hope to graduate a student properly trained as a competent obstetrician or surgeon. The clinical material needed for obstetrics would be tremendous and entirely out of proportion with that available for the other important clinical subjects of the curriculum. A few schools are so fortunate that they can provide 100 cases for each of their students to attend, a number which many of us feel is the minimum which an applicant for medical licensure should have seen, but a very small fraction of that necessary for training an obstetrician. Yet it would be unfair to require any student to see so many cases if it were certain that he would never practice any obstetrics; state boards usually require attendance only on twelve or fifteen cases from the applicant for medical licensure.

Gynecology, however, is given in a very sketchy way considering the importance it bears to general practice. The course usually consists of sixteen lecture periods, supplemented by laboratory exercises in gynecologic pathology, and a touch course of a few weeks' duration in the dispensary. The operative side of the subject is dismissed with brief discussion of the salient features of the technic, on the ground that gynecology is a specialty and, as such, its technic properly belongs in the interne year. The students are not encouraged to watch the operations except to visualize the pathologic anatomy. Few students, however, see any gynecology in their hospital year in this day of "straight interne services," and with the rapidly rotating type of interneship they are on the gynecologic wards for a very short time. And yet nearly one-third of all the major surgical work in general practice is for gynecologic conditions.

The above shows that our medical schools are really only undergraduate institutions, able to give the student a thorough training in the groundwork of medicine, but unable to prepare him to begin general practice immediately after graduation. The plan of teaching assumes that the student will later supplement his work by hospital interneships in which he may learn the handicraft or mechanical art of medicine. Training of this trade-school type is necessary both for the student's development and the protection of the community. It can be learned only in properly planned interneships of at least two years' duration. The general practice of medicine includes major work in obstetrics, gynecology, and surgery, none of which the young physician has a moral right to attempt unless he has had a sufficient hospital or trade-school training.

Anyone who reviews the present teaching plan must admit that the student receives a very broad medical education upon which he may build a better understanding both of disease and of life to make his professional work a joy instead of merely a means of earning a living. One also must find that, in spite of the tremendous amounts of money spent for medical education in recent time, our schools are now utterly unable to turn their students out properly equipped to practice general medicine. Yet this does not prevent them from giving the graduate a diploma entitling him to take the state board examination for a license to practice medicine immediately. The schools admit that hospital work is necessary before the student has a moral right to practice obstetrics, major surgery, or gynecology, but make no concerted effort to provide the proper graduate training or to compel the student to obtain one.

As the law now stands, any physician possessing a state license to practice may undertake any legal type of medical work his patient allows him to do. The evidence is clear that it is time that the medical diploma and the right to practice should be divorced as completely as are religion and the state; the only alternative is that the qualifications for a medical diploma be revised and extended. For many years, solicitors, lawyers, and barristers have practiced law in England, with rights to practice clearly defined for each of the three divisions. Why do we not license the physician to practice only in the departments in which he has had proper technical training, and license separately for practice in internal medicine and minor surgery, or in obstetrics and gynecology, or in major surgery?

Left to the natural course of events, years may pass before this glaring fault in our system of medical education is corrected. Medical policies are extremely conservative. It took seventy years before the American Medical Association won its fight to drive out the proprietary medical schools which all admitted were a blot on education.

Yet such a change in medical licensure is bound to come, forced by bad results in obstetrics, gynecology, and surgery in the hands of those with inadequate training, unless the schools lengthen their clinical courses and train all the pupils in all handicrafts of medicine.

Justin Miller well says that "the purpose of professional licensure is to secure to society the benefits that come from the services of a highly skilled group, and on the other hand, to protect society from those who are not highly skilled, yet profess to be . . . For the present, at least, society seems willing to permit the medical and legal profession to work out their own destinies . . . How long this attitude of society may prevail will undoubtedly depend on how convincing shall be our demonstration of willingness to render the highest type of service."

This Society has led many great movements for the advancement of the public health and welfare. A Fellow and past president of the Society founded the American College of Surgeons and a great medical journal. The American Society for the Control of Cancer owes its origin to our discussions. Our Fellows have been most important factors not only in the White House Conference but also in all others of the many great organizations working for the improvement of maternity conditions. They have led the fight demanding evidence of proper minimum qualifications before one may be listed as a specialist. Their hospitals long since have been developed for the training of competent obstetricians and gynecologists. A new opportunity for public good has arisen. Some one should organize our hospitals as proper graduate institutions and suitably train the great group of untrained graduates who expect to enter general practice.

Rhemann, F.: The Justification of Prophylactic Plastic Operation for Double Uterus, Monatschr. f. Geburtsh. u. Gynäk. **97**: 1, 1934.

The author is of the opinion that it is unnecessary to operate upon most women who have double uteri. The incidence of complications in labor is relatively low in spite of some reports in the literature. Thus Szathmary reported only two cases of uterine rupture in a series of 73 cases of labor in such women. The activity of the uterus during labor is normal as evidenced by the fact that there were only 3 cases of uterine atony.

As regards dysmenorrhea, the author points out that a large number of women without uterine abnormalities also have a great deal of pain at the menstrual periods. Thus far, the Strassmann plastic for double uterus has been performed 37 times and in 11 cases was followed by pregnancy. The author believes that in cases of double uterus an operation is justified only when this anomaly is responsible for habitual abortions or premature labors, and the patient seeks relief for these reasons.

J. P. GREENHILL.

GRANULOSA CELL TUMORS OF THE OVARY*

A Clinical and Pathologic Study of 36 Cases

Emil Novak, M.D., and James N. Brawner, Jr., M.D., Baltimore, Md.
(From the Gynecological Department, Johns Hopkins Medical School)

A STRIKING illustration of the slowness with which new knowledge permeates the medical profession is to be seen in the case of granulosa cell tumors of the ovary. Within the past few years this group of neoplasms has been so much discussed by gynecologic pathologists that one might get the impression that they constitute a newly described type of growth. As a matter of fact, the pathologic characteristics of these tumors were fully described more than twenty years ago, while during many years before and after this a considerable group of more or less clearly defined instances of the lesion had been reported, though often under other names. The present common designation of these tumors as "granulosa cell carcinoma" was applied more than a score of years ago (Meyer,[1] von Werdt[2]).

The present-day interest in tumors of this variety is due, first, to a realization of the fact that they are not nearly as rare as was once believed; and, second, to the fact that they possess interesting biologic properties not possessed by most other ovarian tumors. It is this latter characteristic especially, which, in this day of feverish interest in gynecologic endocrinology, has stimulated the study of granulosa cell tumors of the ovary.

Historical.—For a crystallization of our knowledge of this important group of tumors we are indebted chiefly to the studies of Robert Meyer,[1] although the paper of von Werdt[2] in 1914 was of great importance as a thorough study of the pathologic characteristics of these tumors, even though this author included in his report of 6 cases 2 which obviously are not of the granulosal type. He appears to have been the first to apply to these tumors the present designation of "granulosa cell carcinoma." To Meyer is due the credit for the theory of histogenesis which is now generally accepted, that of an origin from granulosa cell rests. Von Werdt ascribed their source to the various cell complexes described by Walthard[3] (1903) as occurring in the ovaries of newborn children, and including various other congenital inclusions besides granulosal rests.

The first tumor of this class to be reported is apparently that of von Kahlden[4] (1895), who interpreted his growth as an "adenoma of the graafian follicle." Other reports soon followed (Mengersheusen,[5] Schröder,[6] Blau[7]) of tumors of the von Kahlden type, while a considerable number of cases reported as of follicular

*Note: For lack of space it is necessary to omit the clinical case reports, with illustrations of the pathology of these cases and the complete bibliography, but these may be found in the author's reprints as well as in the current volume (1934) of the Society's Transactions.

origin were obviously, when analyzed, of very different character (Brenner,[8] Gottschalk,[9] Voigt,[10] Ingier[11]). In the literature one often finds reference to much earlier reports, such as those of Acconci,[12] Emanuel,[13] Liepmann[14] and Polano,[15] but these do not conform to the granulosal type, being, for the most part, secondary ovarian cancers.

In all of these reports there was much discussion as to the presence of certain cells which resembled primordial ova and which were so considered by one group of observers, while others interpreted them as produced simply by degenerative cystic changes, the view now quite generally accepted. The paper of Brenner is of special interest in that it included a description of the tumor now generally designated by his name (the Brenner tumor or oöphoroma folliculare), but differing from the granulosal growths in histogenesis, pathology, and biologic characteristics.

After these earlier papers there was a slowly increasing number of case reports until very recent years, when the newer knowledge of the physiologic capacities of these tumors, first emphasized by Meyer, has increased the interest in them, so that now probably something like 150 have been reported. In the American literature there have been publications on the subject by Strauss,[16] King[17] Robinson,[18] TeLinde,[19] Taussig,[20] Schulze,[21] Wolfe and Kaminester,[22] Dailey,[23] and others, and three papers by one of the present authors (Novak).[24] It would be difficult, and probably of no great value, to attempt a tabulation of all the reported cases because of the difficulty of appraising properly many of the cases reported in the older literature, especially where good illustrations are lacking.

Material of Present Study.—The present study is based upon 36 cases which have been observed in our laboratory, 20 of these coming from the gynecologic clinic of the Johns Hopkins Hospital, the others being sent in from outside sources. In some of the latter only one or more slides were available for study, so that the study of these could not be considered complete. To avoid duplication in the literature, it should be added that the present collective study includes a number of cases which have already been reported. Among these are 3 cases reported by TeLinde,[19] 6 reported in the two papers by Novak,[24] 2 by Wolfe and Kaminester,[22] and 1 by Dailey.[23] Of our own cases, a number date from the older records of the laboratory, having been revealed in a recent resurvey, not yet complete, of our old material.

PATHOLOGIC ANATOMY

Gross.—There are wide variations in size of the granulosa cell tumors which have been reported. The smallest have been only a few millimeters in size, while others have been so large as to almost fill the abdominal cavity. As a rule, the tumors, as they come under observation, are of moderate size, more or less ovoid or kidney shaped, with smooth outer surface, though often more or less lobulated (Figs. 7 and 16). On cut section, the tumors may be almost or quite solid, especially if they are small, or they may show one or many cystic

cavities. The latter are usually of moderate size but may be very large. The solid portions of the tumor are of granular consistency, not infrequently trabeculated, and often show areas of yellowish hue.

Microscopic.—The extreme variability of the microscopic pattern is chiefly responsible for the confusion of nomenclature and classification of a considerable group of ovarian tumors which are now accepted as having a common histogenesis from granulosal tissue. Indeed, certain tumors of typical sarcoma-like pattern, with little or no resemblance to granulosa tissue, must apparently, as we shall see, be classed under this head. In the great majority of cases, the morphologic resemblance of the constituent cells to granulosal cells and the evidences of growth characteristics identical with those of granulosal tissue constitute the most important criteria for diagnosis.

The extreme variability of microscopic pattern exhibited not only by different tumors, but by one and the same tumor in different parts, makes it very important to study numerous blocks, in order to derive an intelligent impression of the tumor as a whole. In perhaps the most common variety, the granulosa cells show a prevailing tendency to arrange themselves in small clusters of rosettes around a central lumen, so that there is a resemblance to primordial follicles (Fig. 9). At times large masses of granulosa cells may be seen surrounded by a theca-like capsule of stroma. Often there are found in these epithelial masses numerous small areas of cystic liquefaction, resembling the Call-Exner bodies so characteristic of granulosa growth in such animals as the rabbit. The cells around the small cystic cavities are frequently found to be arranged in a curious antipodal fashion which has been much stressed by Meyer, the nuclei of the inner layer being placed close to the central lumen, those of the outer layer away from it, toward the periphery. Between the two there may be only a thin zone of degenerated cytoplasm, or there may be a number of layers of well-preserved cells.

The content of the cystic cavities often bears a superficial resemblance to the primordial egg, with which it was commonly confused by earlier writers, although agreement is now quite general that it represents a secretory or degenerative liquifying process. The same process may be seen in other types of ovarian cancer, as in the so-called "medullary carcinoma with ovum like cells." Not infrequently there may be a large central cystic cavity surrounded by perhaps many layers of granulosa, so that there is a decided resemblance to large graafian follicles. In still other cases the cystic cavities may again be very large but with perhaps only a thin layer of granulosal epithelium. It will thus be seen that these folliculoid tumors may present either a finely folliculoid ("microfolliculoid") appearance resembling primitive follicles or a "macrofolliculoid" picture not unlike that of large mature follicles, with either solidly epithelial, cystic, or partly cystic

content. An occasional picture in granulosa cell tumors is one in which there are large diffuse fields of granulosa cells, with often little or no suggestion of a folliculoid pattern, so that this variety may well be spoken of as the diffuse or parenchymatous type.

The tumor described by von Kahlden[4] in 1895 was of the folliculoid type in at least a part of its structure. In other parts, as may be seen from the illustration accompanying the paper, the microscopic appearance was quite different, and the difference is produced by connective tissue invasion of the granulosal masses, producing the tumor type which has received the designation of cylindroma. The latter is characterized by a splitting up of the epithelial masses into cylinders or columns of various size, often anastomosing with each other (Figs. 3 and 4). It is unusual not to find some evidences of connective tissue overgrowth, with hyaline degeneration, in granulosa cell carcinoma, and the extent of this accounts for many of the variations presented by these tumors. The cylindromatous pattern, therefore, is perhaps the most common of all. All sorts of bizarre patterns may be encountered. In some cases the invasive connective tissue overgrowth splits up the epithelium into narrow zigzag cords, so that a pattern is produced which has been compared to that of moiré silk, or to the disordered rippling of water under the influence of rapidly succeeding waves. In still other instances the epithelial growth is given the gyriform appearance of an elaborate scrollwork.

In extreme grades of this connective tissue invasion and degeneration, the growth may even be given a distinctly adenomatous appearance, the thin epithelial strands showing an involved arrangement resembling adenoma. This is well shown in our Cases 1 and 26, and also in one of Habbe's series[25] (Fig. 10). In any of these types one often finds long cordlike or tubular outgrowths, sometimes resembling the sex cords of early gonodal development, but often distinguished by a characteristic palisade-like arrangement of the epithelial cells.

A striking feature of granulosa cell tumors is the fact that not infrequently one finds a transition from the more typical epithelial areas into areas which cannot be distinguished from sarcoma (Figs. 6 and 12). This fact is of great significance as regards histogenesis and classification, as will be discussed below. In some tumors, as a matter of fact, the sarcoma pattern is the prevailing one although thorough study of the entire tumor will usually show one or other of the more characteristic epithelial features already discussed.

Finally, we have been much interested in the possibility of a lutein-like transformation of some of the cells in the exceptional case of granulosa cell carcinoma, although this subject will receive separate consideration below.

The degree of histologic malignancy in granulosa cell tumors is quite variable and does not seem to be clearly related to the degree of clinical malignancy. In some tumors there is little evidence of anaplastic change, and mitoses may be few. In others there may be marked disparity of cells and nuclei, hyperchromatosis, and numerous mitoses. The tumors are usually quite vascular and often exhibit marked dilatation of the lymph channels.

HISTOGENESIS

The similarity of the constituent cells of the granulosa cell tumors to the normal follicular epithelium would at once suggest that the origin of the tumor is to be sought in some phase of follicular development. The view that such neoplasms may arise from the adult follicle has been virtually abandoned. To mention only a few objections to such a theory, one must recall, first of all, as has been urged by Meyer, that the follicular epithelium is a satellite tissue of short life and that this is dependent upon the life of the ovum. It would seem difficult to believe that such a tissue could give rise to neoplasms. Again, the fact that so many granulosal growths occur in old women, long after the period of follicular activity, would speak against such a theory.

Without going into details, suffice it to say that there is now quite general acceptance of Meyer's view that granulosa cell tumors arise from granulosa cell "rests" (granulosaballen), left over from the early oophorogenetic phase of ovarian development. That such rests occur can be readily demonstrated in the study of the ovaries of young individuals, and especially of children, though they may be found also in later life (Fig. 1). The findings of such remnants in close relation with early granulosal tumors constitutes strong circumstantial evidence as to the source of the latter, and such observations have been made by Meyer and others.

No adequate idea can be obtained as to the nature of these tumors or as to the reason for their protean histologic structure unless one is familiar with the early developmental changes in the ovary. These have been reviewed in a previous paper (Novak and Long), and here it will be sufficient to emphasize only one point. Contrary to the older viewpoint sponsored by Felix and Winivarter, evidence has accumulated in recent years, especially in the work of Fischel[26] and Politzer,[27] to indicate that the covering epithelium of the ovary is really not a germinal epithelium in the sense of producing germ cells or, by its supposed invasive invagination, the follicular epithelium as well. On the contrary, it seems now to have been fairly well established that the granulosa cells are formed in loco from the ovarian mesenchyme, from which likewise is formed the theeal and stromal tissue of the ovary.

The importance of this observation lies in the fact that it offers an adequate explanation of the apparent intermutability of the ovarian epithelium and connective tissue, and of the frequent transitions between the two in granulosa cell carcinoma, as will be discussed below. The finding of areas of sarcoma-like appearance in granulosa cell carcinoma is thus easy to understand. Furthermore, we can also understand that the granulosal and stromal elements, both derived from the same parent tissue, may have the same physiologic capacity to produce the female sex hormone, so that even an apparent sarcoma can exert biologic influences no less potent than an epithelial tumor of the same histogenesis.

Viewed in this way, the concept of granulosa cell tumors would include also certain tumors of connective tissue type, and it would seem unnecessary to speak of "thecoma" as a special type of neoplasm, as has been done by Loeffler and Priesel[28] and more recently by Melnick and Kantner.[29] The term "granulosa cell carcinoma" can also properly be extended to include cases in which a lutein-like transformation of some or all of the cells has occurred (folliculome lipidique of Lecène,[30] and possibly luteoma).

PATHOLOGIC TYPES

On the basis of what has been said as to the microscopic structure of granulosa cell tumors, various types may be described, always with the common mingling of these in the same tumor in mind. The differentiation of varieties is well worth while if for no other reason than that it gives an opportunity of pointing out the possibilities of confusion of each of these with other ovarian tumors.

The folliculoid varieties would seem fairly distinctive, and there would seem to be little reason for errors of diagnosis with this group, though in past years they were not infrequently reported as adenocarcinoma.

The cylindromatous variety, which one finds often designated in the older literature as cylindroma of the ovary, has probably been more frequently misinterpreted than any other group. Cases of this type have often been reported as endothelioma or as alveolar carcinoma.

The diffuse variety usually presents features which permit ready recognition and easy differentiation from the types of medullary carcinoma, such as the obvious morphologic resemblance of the cells to granulosal epithelium and the presence of the characteristic growth features of the latter (such as the tiny areas of cystic degeneration). Almost always, moreover, other sections of the same tumors show transition to the folliculoid or cylindromatous patterns. The latter statement applies also to the rare adenoma-like pattern, which in individual

fields might be very puzzling to one who had not had the opportunity of previous study of such cases.

The sarcoma-like tumors cannot be distinguished in individual areas from sarcoma of other types though, with few exceptions, other parts of the tumor clear up the matter of histogenesis. From what has been said as to the origin of granulosa cell tumors, from the fact that both the follicular and thecal cells probably have a common origin from the embryonic ovarian mesenchyme, and from the further fact that, as we shall see, the biologic properties of the tumors seem to be the same regardless of whether the constituent cells are epithelial or connective tissue in type, there would seem to be no reason for distinguishing a small group of them as "thecoma," as has been done by Loeffler and Priesel,[28] and more recently by Melnick and Kantner.[29] This is particularly true in view of the obvious intermutability of the cells, as shown in the transitions demonstrable in one and the same tumor.

Exactly the same picture is seen in our Case 28, in which the structure of the tumor is that of sarcoma, although there are islands and bands of cells which morphologically resemble lutein cells and which, on differential staining, show large amounts of lipoid substance (Figs. 12 and 13). The interesting feature is that the tumor produces both folliculin and the corpus luteum hormone, if one may judge from the microscopic appearance of the endometrium.

A small group of these lipoid-containing tumors, with usually a greater or less degree of lutein-like transformation of the cells, has now been reported. For their six cases Loeffler and Priesel chose the designation of "fibroma thecocellulare xanthomatodes ovarii," and their view that such tumors are of thecal origin, and are to be considered quite apart from the granulosa cell group, has been adopted by Melnick and Kantner, who reported two similar cases. With this view we do not agree, feeling that they should be looked upon as a species of granulosa cell neoplasm, for the reasons above stated.

We believe, furthermore, that in this same category is to be placed the "folliculome lipidique" described by Lecène in 1910 and again in 1927 (Moulonguet-Dolèris).[30] Another instance of this has recently been reported by Plate,[31] whose illustrations leave little doubt of the granulosal nature of the growth. It is this general group which must be correlated with the clinical observation that the uterine mucosa, even in postmenopausal patients, may at times show a marked secretory or even decidual picture. This endometrial reaction, so far as we know, can be produced only under the influence of progestin, and hence all such cases should be studied carefully to determine whether or not the tumors belong to the lipoidal or lutein-like variety. A number of cases have been described with this functioning reaction in the endometrium. Our Case 28 is of this variety, and similar observations

have been made by Arnold, Mathias and Koerner,[32] Klaften,[33] and others, in addition to the above mentioned case of Plate.

To pursue this subject just a bit further, one may naturally inquire whether we may not consider the so-called luteomas, made up entirely of what are apparently lutein cells, as merely a finished stage of this lutein transformation of primarily granulosal tumors. This is particularly true because it is hard to believe that lutein cells, any more than adult granulosal cells, would give rise to neoplasms. Our knowledge of the real nature of luteomas is too meager to justify any statement as to their exact relation to the granulosal cell group, especially when we bear in mind the confusion existing in the literature because of the difficulty of distinguishing luteoma from adrenal tumors of the ovary (hypernephroma).

CLINICAL CHARACTERISTICS

As with ovarian tumors in general, there may be certain symptoms due to the presence of the growth, such as pain or discomfort in the lower abdomen, and, if the tumor is sufficiently large, the presence of a mass which the patient herself may note. These rather obvious symptoms need no discussion here, and we shall discuss only a few of the more distinctive manifestations.

Age Incidence.—The ages of the 33 patients in whom this knowledge was available are shown in Table I. It will be seen that 5 occurred

Table I. Age Incidence of 33 Cases

AGE IN YEARS	NUMBER OF PATIENTS		PERCENTAGE IN DECADES
1- 5	3	5	15.15
6-10	2		
11-15	0	1	3.03
16-20	1		
21-25	2	4	12.12
26-30	2		
31-35	3	7	21.21
36-40	4		
41-45	4	12	36.36
46-50	8		
51-55	1	3	9.10
56-60	2		
61-65	1	1	3.03
66-70	0		

in children before puberty, and in all there were manifestations of precocious puberty and, with one exception (Case 32), menstruation. In only 6 of our group were the patients definitely beyond the menopause although in 10 others the patients were in the fifth decade. The statement so frequently made that granulosa cell tumors of the ovary occur most often in elderly women is not borne out in this series, nor

in the recent group of 12 cases reported by Kleine.[34] Only 3 of the latter were beyond the menopause, and a number were very young.

Menstrual Disturbances.—The effects of these tumors upon the menstrual function are what one would expect from the production of excessive amounts of folliculin, as will be discussed below. Speaking generally, tumors before puberty produce precocious menstruation; those

TABLE II. CASES WITH PRECOCIOUS PUBERTY

CASE NO.	AGE	VAGINAL BLEEDING
8	5 yr.	1 wk. duration
13	7 yr.	For 10 mo., every 1-3 mo., flow 1-4 wk.
19	7 yr.	3-8 day flow every 28 days for "several months"
23	3 yr. 11 mo.	"Regular menstruation" for 4 mo.
32	4 yr.	For several days 3 days after operation

TABLE III. MENSTRUAL DISTURBANCES

CASE NO.	AGE IN YEARS	DURATION OF DISTURBANCE	MENSTRUAL INTERVAL	DURATION OF FLOW	AMOUNT OF FLOW	AMENORRHEA
1	32	1 yr.	2 wk.	--------	Normal	9 mo.
2	45	2 yr.	1-5 wk.	1-3 wk.	Profuse	None
3	44	6 yr.	1-9 mo.	1-6 wk.	Profuse	4 mo.
4	49	6 yr.	1-3 mo.	--------	Profuse	None
5	50	4 yr.	4 wk.	2-3 wk.	Profuse	None
9	47	2 yr.	Irregular	--------	Scant	6 wk.
14	39	6 mo.	Irregular	--------	Normal	None
16	43	1 yr.	--------	Prolonged	Profuse	None
20	32	10 mo.	4 wk.	6 days	Profuse	None
21	38	6 yr.	--------	--------	--------	6 yr.
24	48	3 yr.	--------	--------	--------	3 yr.
25	27	3 mo.	--------	3 mo.	Profuse	None
26	40	2 wk.	--------	2 wk.	--------	None
27	34	1 yr.	2 wk.	--------	Profuse	None
29	29	7 mo.	--------	--------	--------	7 mo.
30	25	-----	"Shortened"	7-15 days	Profuse	None
31	43	5 mo.	2-6 wk.	--------	Profuse	None
33	20	4 yr.	1-6 mo.	2-3 days	Scant	6 mo.
35	40	5 yr.	4 wk.	3-5 days	Profuse	5 wk.
36	46	1 yr.	Irregular	--------	--------	None

TABLE IV. POSTMENOPAUSAL BLEEDING

CASE NO.	AGE WHEN ADMITTED	AGE OF MENOPAUSE	DURATION OF BLEEDING	INTERVAL	DURATION OF FLOW	ENDOMETRIAL HYPERPLASIA
6	56	51	3 yr.	3 wk.	1-7 days	Yes
7	46	45	4 mo.	4 wk.	3-7 days	Yes
15	65	43	6 mo.	4 wk.	"Few days"	Yes
17	50	42	4 yr.	1-3 wk.	4-5 days	Uterus not removed
18	50	46	2 yr.	6 wk.	2-3 days, later 5 mo.	Yes
28	57	47	6 mo.	4 wk.	3-4 wk.	Yes

during reproductive life bring about disturbances quite analogous to those so characteristic of hyperplasia of the endometrium (menstrual excess with amenorrhea at times), while tumors after the menopause tend to reestablish a menstrual or pseudomenstrual type of bleeding. Tables II, III, and IV enumerate the menstrual disorders in those patients in whom such symptoms were noted. They bear out what has been said above as to the general nature of these menstrual effects. The common, though not by any means invariable, picture presented by the endometrium is that of hyperplasia.

Of especial interest are the 8 cases in which periods of amenorrhea, at times very long, had been noted before the patient came under observation. Similar observations have been made by Habbe[25] and others. Plate suggests that this symptom is perhaps to be linked up with the finding of lipoidal changes in the tumor, corresponding to the pseudopregnancy which may be produced by persisting corpus luteum cysts. We do not believe that this necessarily follows, for a similar occurrence of amenorrhea may be seen in cases of endometrial hyperplasia, in which corpora lutea are notoriously absent. The alternation of bleeding and nonbleeding phases is more likely to be due to the reciprocal effect of the ovarian folliculin upon the anterior hypophyseal sex hormones, as suggested by Novak[35] in a recent paper. Furthermore, in our Case 28 there was no amenorrhea, even though a lipoidal type of tumor was present, with secretory changes in the endometrium.

Other Biological Effects.—Aside from the effects upon menstruation, there has been noted, in a certain number of reported cases, a stimulating effect upon the structure and function of the breasts. In all our cases in children, there was marked mammary overgrowth, though no secretion was present. In older patients similar hypertrophy, with the secretion of a colostrum-like fluid in some instances, has been observed by Müllerheim,[36] Plate,[31] and others. In a few cases (Klaften,[33] Plate) virilism and hirsutism have been described, but these must be looked upon as not especially characteristic, and this occurrence cannot be satisfactorily explained in the present state of our knowledge of endocrinologic relationships.

In children, before puberty, and again in women beyond the menopause, there are seen striking effects upon the secondary sex characters. This is shown especially in the sex precocity brought about in young children. As the effects of these tumors upon sex characters have been described in a previous paper they need not be further alluded to here. In tumors occurring during reproductive life, when the patient's secondary sex characters are already in full bloom, one would not expect to find such striking manifestations of this type as are seen when the tumor function is projected against the comparatively bare sex background of puberty or old age.

The special biologic effects of these tumors are due to the fact that they secrete folliculin and, in some cases, progestin also. The folliculin effect has been amply demonstrated by the production of estrous effects in castrated mice following the injection of extracts of the tumor (Meyer, Klaften, Neumann[37]). Quantitative studies of the hormone content of the urine (Schuschania[38]) have shown much larger quantities than in the urine of normal women. In only one case, reported by Clauberg and his associates,[39] was progestin sought for in the urine, and without success, as might have been expected from the absence of this hormone in tissues other than the corpus luteum.

It is of interest to note that the Aschheim-Zondek reaction (HVH I) has been positive in a number of instances (Dworzak and Podleshka,[40] Pahl[41]), though this mild response is not of course conclusive. In Pahl's case, however, both the second and third degrees of reaction were positive (HVH II and III). This is significant in view of what has been said as to the possibility of lutein-like changes in the tumor cells. Just how these are to be explained we can only speculate. The frequent finding of prolan A in the urine of these patients suggests that there must be some interaction between the ovary and the anterior lobe and that the luteinizing factor of the latter brings about the occasional transformation of granulosal into lutein or lutein-like cells. After all, the normal lutein cell of the corpus luteum is only a modified granulosa cell, and for that matter it is possible, as some believe, that progestin is only a modification of folliculin. If this is true, it is not difficult to understand the occasional transformation occurring in the granulosal tumor while the effects of the tumor hormones are in conformity with what we know of these effects upon the genital mucosa and sex character development generally.

Malignancy.—There has been rather general agreement that the degree of malignancy of granulosa cell carcinoma is much less than that of ovarian cancer in general, and the evidence certainly supports this view. It would seem, however, that the degree of malignancy is considerably greater than we would gather from most authors, many of whom speak of these tumors as relatively benign. The earlier case reports, dealing as most of them did with descriptions of single cases or small groups of cases from the pathologic standpoint, were not of much value in determining the ultimate fate of the patients, and the same criticism can be made of even recent cases. It can be made also of our own series, for many of our cases were observed many years ago, and no adequate follow-up has been possible. In spite of this, at least 9 of our patients showed unmistakable evidence of malignancy, either in the picture presented at operation (6 cases) or in the development of recurrences (3 cases), sometimes surprisingly soon after operation (see Table V). These 9 cases were from a group of 32 in which accurate data were available, giving a clinical malignancy rate of 28.1 per

cent, much higher than the 5 to 10 per cent rate suggested by most of the reports available in the literature. It is worthy of note that instances of recurrence and metastasis are apparently being reported with increased frequency as interest in these tumors has increased. Such cases have been reported by Aschner,[42] Klaften,[33] Soltmann,[43] Bagger,[44] and others. While in most instances the recurrence has been local and peritoneal, there have been several observations of metastasis to the bones. (Soltmann.)

TABLE V. MALIGNANCY

CASE NO.	AGE	METASTASES AT OPERATION	ASCITES	RECURRENCE
1	32	Generalized peritoneal	Marked	--------
4	49	Omentum	None	3 yr. later
6	56	None	None	1½ yr. later
9	47	None	None	7 yr. later
20	32	None	With recurrence	2½ mo. later
31	43	Peritoneal, inoperable	--------	--------
33	20	Inoperable	--------	--------
34	24	Generalized peritoneal	Marked	--------
35	40	Omentum and broad ligament	--------	--------

For 32 cases with clinical data, percentage of malignancy, 28.1

Diagnosis.—As a rule the tumor can be readily demonstrated by bimanual or abdominal examination, and, for that matter, has often been noted by the patient herself. In women during the reproductive epoch, the granulosal nature of the neoplasm is usually not suspected until operation, and perhaps not even then. When there is any clinical suspicion of the character of the tumor, quantitative studies of the hormone content of the urine may prove of value.

It is in childhood and in the postmenopausal years that the preoperative diagnosis of the nature of the tumor can most often be made, at least presumptively. This is because of the physiologic and biologic effects produced by the growth, which stand out sharply in patients at these ages, as already emphasized in a previous paragraph. If an ovarian tumor is demonstrable in a child with precocious menstruation and puberty, it is very likely to be of the granulosa cell type. Again, if a tumor is found in a patient well beyond the menopause, associated with periodic and perhaps pseudomenstrual bleeding, it is almost sure to be a granulosa cell cancer. The likelihood is converted into almost absolute certainty if a diagnostic curettage yields a frankly hyperplastic endometrium. In both these groups, hormone studies are of even greater value than in the case of tumors encountered in patients during reproductive life.

Our Case 28 is of especial interest from the standpoint of diagnosis because here no ovarian tumor, or ovarian enlargement, could be made out even on examination under anesthesia. And yet the endometrial picture pointed so clearly to the probability of a granulosa cell growth, that a "physiologic diagnosis" of this type of tumor was made. This

was confirmed after removal of the organs, the left ovary showing the small granulosa cell tumor depicted in Fig. 11. The common cause of postmenopausal hemorrhage is adenocarcinoma, and diagnostic curettage is necessary to make the diagnosis. If the curettings show definite hyperplasia, with no suspicion of cancer, it would seem that laparotomy is indicated, even though no ovarian tumor can be palpated.

Treatment.—The treatment of these tumors is of course essentially surgical. The extent of operation must be based upon our concept of the degree of malignancy of these tumors, concededly less than that of other ovarian neoplasms. Many patients have remained well after simple unilateral salpingo-oophorectomy, but we believe that such a conservative plan should be followed in only a limited group, in view of the fact that recent reports indicate a greater degree of malignancy than had been previously assumed. In young patients the removal of the adnexa on the affected side alone would seem permissible, but such patients should be carefully followed for evidences of recurrence. In the more common case in which the patient has already lived all or most of her reproductive life, the definite and as yet not accurately determined degree of menace presented by these tumors would seem fully to justify a more radical procedure, i.e., hysterectomy with bilateral removal of the adnexa. This would certainly apply to the frequent cases seen in women beyond the menopause.

In view of the radiosensitivity of granulosal tissue to radiotherapy, it would be expected that these tumors should likewise be very responsive to this form of treatment although only a few reports have been made on this point.

For the present it would seem wiser to restrict radiotherapy to the treatment of inoperable or recurrent tumors, or to combine it preoperatively or postoperatively with surgery in the treatment of removable tumors.

26 East Preston Street

Nielsen, M.: Isolated Tuberculous Infection in a Multilocular Ovarian Cyst, Acta Obst. et Gynec. Scandinav. **13:** 228, 1933.

Tuberculous infection of ovarian tumors is a very rare affection, like tuberculous infection limited to the ovary, and probably not more than 40 cases of this condition have been reported in the literature. In the case reported by Nielsen the infection must be said in all probability to have been hematogenous, as the tubes as well as the peritoneum were found to be normal.

Only 6 cases of isolated metastatic tuberculosis in ovarian tumors are on record.

J. P. Greenhill.

ILIAC LYMPHADENECTOMY WITH IRRADIATION IN THE TREATMENT OF CANCER OF THE CERVIX

FRED J. TAUSSIG, M.D., ST. LOUIS, MO.

IN THE effort to effect a cure in cancer of the cervix we are faced by two difficulties, one is the direct extension of the disease to the parametria and surrounding organs, the other is the metastasis along the lymphatic channels to the tributary lymph glands. By means of a radical hysterectomy in the early cases and by means of a combination of radium and x-radiation in those with beginning parametrial infiltration, we can reasonably hope to cure about half the cases. When, however, there has occurred a metastasis to the lymphatics, the question of a cure becomes much more problematical. On the one hand, the thorough lymph gland removal, if combined with a radical hysterectomy, is attended by a prohibitive primary mortality as even the most skillful surgeons found out to their regret. On the other hand, it has been an almost universal experience in the treatment of cancer of all organs that metastases to the lymph glands are markedly insensitive to irradiation. Hence in spite of the superficial location of the lymph glands in breast, mouth, vulva, and skin cancer, cancer therapists have preferred surgical removal to any form of radium or deep x-ray treatment. It was this situation that induced me in October, 1930, to attempt a new mode of attack in these more advanced cancers of the cervix. This consisted of irradiation of the cervix and surrounding tissues and the surgical removal as far as feasible of the tributary pelvic lymph glands.

If in the course of the three and a half years that have since elapsed I have performed this operation in only 26 patients, this is partly due to the fact that my clinical material has not been very large and partly to my desire to select for this procedure such cases as would present no serious operative difficulties. It was evident that no method of treatment was justified that was attended by a high operative mortality. For this reason all Group IV, hopelessly advanced cases, were excluded. Group I cases were also excluded since the percentage of lymph gland involvement was relatively low, and the results of measures now employed were reasonably satisfactory. Hence my cases were limited to Group II and Group III. I should like to make it clear, however, that under Group II, I included only cases somewhat more advanced than the old so-called "borderline" cases. Some persons would have classified many of my cases as Group III. In none of them could hysterectomy have been performed without cutting through cancerous tissue or in-

juring neighboring organs. As Group III cases I have classified those cases in which the infiltration extended to the pelvic wall on one side. Of the 26 patients, 18 fell into Group II and 8, into Group III. In the selection of suitable cases I gave preference to younger individuals in good physical condition, excluding all markedly obese patients and those with heart or kidney complications. Radiosensitive tumors with high malignancy index were also less frequently subjected to this procedure.

The bulk of the pathologic investigations of pelvic lymph gland metastasis in cervical cancer date back to the first decade of this century when the question of the radical Wertheim operation with gland removal was the subject of such acrid debate. It was on the basis of these studies that my operative technic was developed. At first sight these investigations seem to present rather contradictory findings, but when the source of the material (operation, autopsy) is analyzed, this is not true. The reports come almost wholly from the large German clinics where routine serial sections of lymph glands were made in large numbers of patients operated on or coming to autopsy. I have included the work of Brunet, Baisch, Kundrat, Schauta, Mackenrodt, Kermauner, Lahm, Pankow, Leitch, and others. The net results of these studies can be summarized as follows:

1. Cancer is found in from 25 to 33 per cent of lymph glands removed in Group I operable cases, in from 45 to 50 per cent of lymph glands removed in advanced (Group II or Group III) cases, in about 66 per cent (two-thirds) of the cases coming to autopsy (Group IV).

2. Considerable uniformity is manifest in the anatomic spread of lymph gland metastasis. Where lymph gland cancer is present, it is limited in about 95 per cent of the cases to the so-called Stage 1 glands, meaning thereby the iliac triangle or hypogastric glands, the obturator glands, the ureteral or Championnier glands, and the sacral glands. In order of frequency these glands are involved: (1) iliac, (2) obturator, (3) ureteral, (4) sacral. Stage 2 glands include the lumbar aortic glands, the inguinal glands, and the glands over the common iliac vessels. These Stage 2 glands are involved in addition to Stage 1 glands in Group I and Group II cervical cancer in from 5 to 10 per cent of the cases but practically never are involved as a primary metastasis without any cancer in Stage 1 glands.

3. It seems a fairly constant rule that Stage 2 glands became involved only as an overflow after the cancer has filled up glands of Stage 1 distribution.

4. Enlarged, indurated glands do not necessarily mean cancer metastasis, nor do small soft glands exclude such a possibility. Microscopic section is required to establish a positive diagnosis.

5. While glands are most apt to be involved if the parametrium is infiltrated, it may happen that glands are involved without cancer in

the parametrium and the parametrium may be extensively invaded without gland metastasis.

Schauta, in 50 cases coming to autopsy with cancer of the cervix, found carcinomatous lymph glands in 32 cases (64 per cent). Baisch, in 28 operative cases of cervical cancer, removed 45 lymph gland metastases distributed as follows: parametrial or ureteral glands, 11; hypogastric and iliac glands, 26; sacral glands, 2; lumbar glands, 4; deep inguinal glands, 2. Out of these 28 cases, 26 showed cancer in the first-stage glands, 2 showed in addition metastasis in the second-stage glands, but in no case were the second-stage glands involved without the first stage. Brunet found cancer in the lymph glands in 24 out of 47 cases (51 per cent). Schottlaender and Kermauner found in squamous cancer of the cervix that cancer was present in the glands 29 times out of 65 cases studied (45 per cent). The parametrial lymph nodes, known as ureteral or Championnier glands, are often found in pairs, according to Lahm, Kundrat, and others and are more often involved by cancer from the cervicovesical junction than as a direct extension from the cervical canal. Kundrat in 80 operable cases from Wertheim's clinic found parametrial involvement in 44 and lymph gland involvement in 26 (32 per cent). In four cases the lymph glands were involved without evidence of cancer in the parametrium. Leitch investigated records of 915 autopsies in cancer of the cervix and stressed the importance of the interiliac glands in extension of cancer. Lynch says that cancer is occasionally arrested by the lymph glands, hence he believes that "we should do the most thorough operation that each individual patient will stand." Philipp, in reporting results in 108 Wertheim operations with glands removed from 1923 to 1925, found carcinoma present in the glands 16 times (15 per cent) with only 2 free of recurrence in five years whereas in 92 with negative glands, 58 were free of recurrence. Nevertheless, he concludes that postoperative radiation is less effective than gland removal.

On the basis of this pathologic evidence it would seem that if we could remove surgically this Stage 1 group of lymph glands without any considerable operative mortality, a definite increase in the percentage of permanent cures might justly be hoped for. Of these glands the iliac and obturator would be readily accessible after opening the broad ligament and the ureteral gland, while requiring more careful and longer dissection, could then also be excised. Only the sacral glands were situated out of easy surgical reach, but these were only rarely involved. At the same time it was felt that the removal of the adnexa necessary for the exposure of this area might be of added benefit by reducing the uterine blood supply and eliminating the monthly hormonal stimulation in younger individuals. The following plan of operation was therefore devised:

Under spinal anesthesia a midline incision was made. After simple ligation and removal of the right adnexa (Fig. 1), the posterior sheath of the broad ligament on that side was caught with a clamp and the ligament opened up exposing the ureter coursing over the pelvic brim attached to the posterior sheath. The bifurcation of the common iliac vessels into the external and internal iliac branches could then be seen, and tucked in the angle between these vessels was a lymph gland, the

iliac (Fig. 2), the most common site of cancer metastasis. This gland was often so deeply pocketed under the large veins that it could not be felt until it had been teased loose from the surrounding areolar tissue and fat. With a little experience in lymph gland palpation and dissection it becomes a relatively simple matter to free such a gland and lift

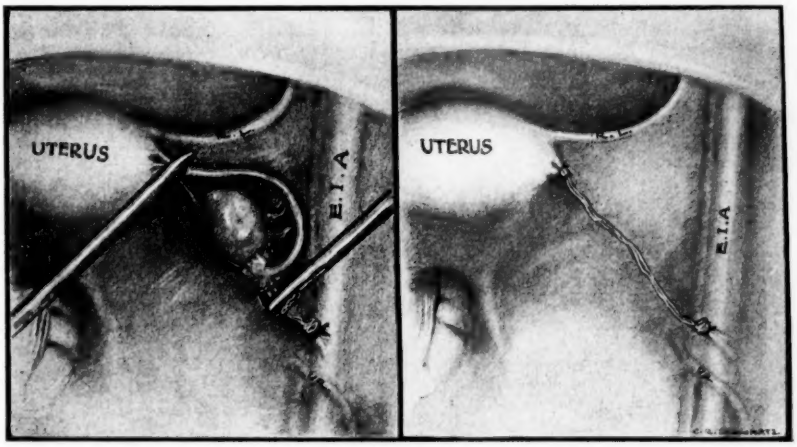


Fig. 1.—Operation of iliac lymphadenectomy. *A.* Ligation and removal of tube and ovary. *B.* Broad ligament unopened with iliac vessels and ureter shimmering through peritoneum. *E.I.A.*, external iliac artery; *R.L.*, round ligament; *Ur.*, ureter.

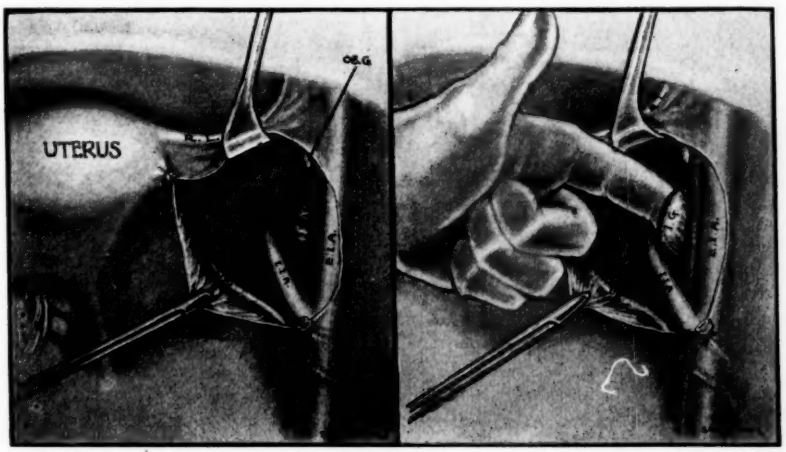


Fig. 2.—Operation of iliac lymphadenectomy. *A.* Broad ligament opened showing iliac bifurcation with gland situated at this point and obturator gland visible at upper angle. *B.* Finger lifting iliac gland from surrounding areolar tissue before clamping nutrient vein. *I.I.A.*, internal iliac artery; *I.G.*, iliac gland; *Ob.G.*, obturator gland.

it up so that the little nutrient vein can be caught and ligated. It is by no means always necessary to ligate these veins, though this is usually preferable. When this gland and its surrounding fat were removed, we could see the obturator nerve shining white and running straight toward the obturator foramen. After passing the finger between it and

the external iliac vessels, it was usually possible to feel an elongated, usually rather round and firm, gland (Fig. 3-A) lying halfway between the iliac bifurcation and the femoral ring. By retracting the round ligament this region was exposed, and the removal of this obturator gland effected without difficulty. If the parametrium was not thickened too much, it was then possible to follow the ureter down to where it

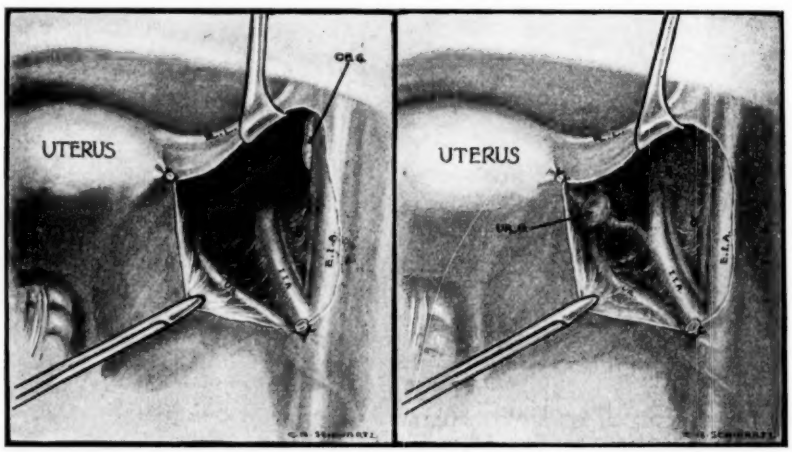


Fig. 3.—Operation of iliac lymphadenectomy. *A.* Iliac gland removed and obturator gland exposed. *B.* Obturator gland removed and enlarged ureteral gland (not usually present) visible over crossing of ureter and uterine vessels. *Ur.G.*, ureteral gland; *Ob.G.*, obturator gland.

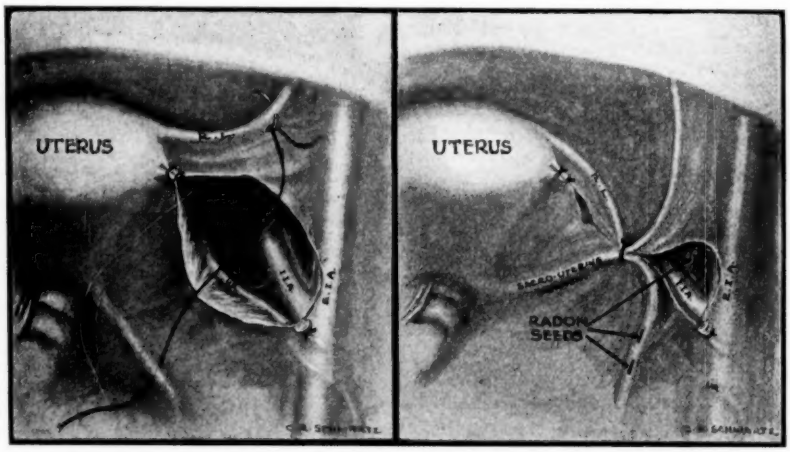


Fig. 4.—Operation of iliac lymphadenectomy. *A.* After removal of all glands, sacrouterine and round ligaments are sutured together to close over dead space and prevent hematoma. *B.* Showing location of radon gold seeds implanted in the outer portion of the sacrouterine ligament and in the loose connective tissue between the iliac vessels, but at a distance of at least 1 cm. from the veins. These seeds are placed before the ligament suture is tied. *R.L.*, round ligament; *E.I.A.*, external iliac artery; *I.I.A.*, internal iliac artery.

crossed the uterine artery. It was at this point that we could occasionally feel a definite round nodule or pair of nodules, the ureteral glands (Fig. 3-B), or glands of Championnier. The removal of these glands was

more difficult since injury to the ureter must be avoided. It was often necessary to ligate the uterine vessels to accomplish this and at times the gland was so surrounded by exudate as to make its removal inadvisable. This was true in 2 out of 7 of my cases. In such instances radium emanation seeds were implanted into the lymph gland.

As to the sacral glands, the relative infrequence of their involvement, their varying location back of the rectum, and the necessity of extensive deep dissection to effect their removal, all led me to refrain from including them in my operative procedures. I feared that if these glands were also excised, the operation would be unduly prolonged and its primary mortality be increased. Hence as a compromise to their removal, following in part the method recently suggested by Dr. Gellhorn, two gold radon seeds of 1½ mc. each were implanted with a trocar along the course of the sacrouterine ligaments. A third radon seed of equal strength was then planted into the loose connective tissue of the iliac bifurcation. In order to prevent the formation of a hematoma in the broad ligament, the connective tissue space that had been opened up, was compressed by suturing the round and sacrouterine ligaments to each other at a distance of 4 or 5 cm. from their uterine insertion (Fig. 4). The remaining wound was closed by a running peritoneal stitch. The same procedure was then done on the other side. The abdomen was closed without drainage. This was usually followed by an intracervical application of radium.

Since this operation usually did not take more than from forty-five to sixty minutes, and since a good exposure with complete intestinal relaxation was a desideratum, in almost all cases the anesthesia employed was spinal novocaine. Naturally, in a procedure of this kind, where we had no previous experience to guide us and were sailing uncharted seas, a certain variability both in type of cases selected and in the method employed was bound to result. Occasionally lymph glands were found at unusual sites. Encouraged by the excellent postoperative course of the earlier cases, the indications were extended to include more advanced cases. The results in this group, however, were far from satisfactory as will subsequently be shown.

Considerable variation also occurred in the irradiation. Preliminary radiation was given in the form of deep x-ray or intracervical radium application in 16 out of the 26 cases. In all but 2 cases radium or radon seeds were applied at the time of the lymph gland resection (radon seeds in 21 cases, radium alone in 3 cases, a combination of the two in 12 cases). The x-ray treatment given usually on four days over a period of ten days totaled 900 milliampere minutes, equivalent to 824 r. units, and was employed in 13 cases. The lowest dose of radium given was 1,600 mg. hr. in a patient with incomplete treatment who died six days after operation and the highest dose was 8,275 mg. hr. where reirradia-

tion was resorted to for a recurrence. The average dose which was maintained in almost every case was 4,250 mg. hr.

The immediate operative result was usually satisfactory. There was rarely any postoperative shock except in the more advanced cases. Dividing the 26 cases into the 16 Group II patients and the 8 Group III patients, we find that in the less advanced group there was one operative death (5.5 per cent), while in the far advanced group there were 3 deaths out of 8 patients (37.5 per cent). The single Group II death occurred suddenly on the sixth day after an uneventful course and was due to an embolus. Temperature, pulse, and respiration taken one hour before death were normal. In this case additional radon seeds had been implanted in the infiltrated broad ligament close to or possibly into the uterine vein. This death can hardly be attributed therefore to the lymph gland resection. Dr. Gellhorn reports a similar fatality where abdominal radon seeds alone were employed. Of the 3 deaths associated with the Group III cases, 2 were due to peritonitis and 1 to fatty necrosis of the liver. There is no doubt that the operative trauma plus the radiation was responsible for their deaths, but it is also true that the cases were too far advanced to be suited to this method of treatment. In general, therefore, I think it is fair to assume that with proper selection of cases and with care to avoid the implantation of radon seeds too close to the large vessels, the immediate operative mortality of this lymph gland resection should be so low as not to serve as a contraindication to our method of treatment.

Too short a time has of course elapsed to judge of the final result but on the whole the outlook is rather encouraging in the Group II cases, but discouraging in the Group III cases. Of the latter only 1 case out of 8 has survived two and one-half years since operation. On the other hand, out of 16 Group II patients, 1 died after operation, 5 died of recurrence from twelve to twenty-one months after operation, 12 are living, 1 with a probable recurrence, and 11 are clinically well for periods ranging from four months to three and one-half years. Table I gives an outline of the results in these groups.

TABLE I

	TOTAL NUMBER	DIED POSTOPERATION	DIED RECURRENT	LIVING RECURRENT	LIVING AND WELL				
					TOTAL	1 YR. OR LESS	1-2 YR.	2-3 YR.	OVER 3 YR.
Group II	18	1	5 (12-21 mo. postop.)	1 (3 mo. postop.)	11 5 ca. gland	3	3 1 ca. gland	3 2 ca. gland	2 2 ca. gland
Group III	8	3	4 (3-9 mo. postop.)		1 ca. in gland			1	
Total	26	4	9	1	12	3	3	4	2

Keeping in mind the fact that cancer in younger individuals is more difficult to cure, it was hoped that this method of combined lymph gland removal and irradiation might prove an advance over previous forms of treatment just in these cases. Hence an effort was made to select primarily younger persons. The average age of the 26 patients was forty and one-half years; 11 were under thirty-five years of age; 7 were between thirty-five and forty-five, and the remainder between forty-five and fifty-eight years. Only 5 of the 26 had entered the menopause. The results in the Group II cases are summarized in Table II.

TABLE II

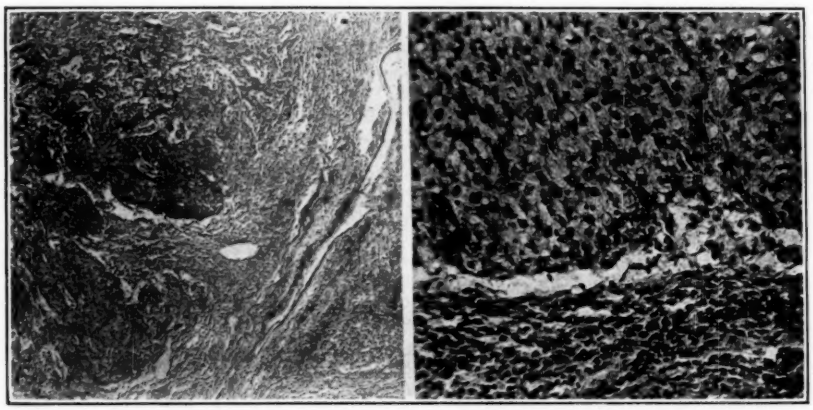
	NUMBER	DIED	RECURRENT	LIVING AND WELL
Under 40 yr.	8	1		7 (2 with ca. in glands)
Over 40 yr.	10	5	1	4 (3 with ca. in glands)
Total	18	6	1	11

It would seem from this that the attempt to improve results in younger women by this method of treatment is deserving of further consideration.

We now come to the crux of our problem. What were the histologic and gross findings in the lymph glands removed at operation? In every case lymph glands were found, but in a few instances they were found on only one side. A total of 85 lymph glands were removed in the 26 cases. These were divided as follows: 24 right iliac, 22 left iliac, 16 right obturator, 16 left obturator, and 7 ureteral glands. Two ureteral glands were found enlarged but not removed because too closely adherent to the ureter. In no case was the adhesion to the iliac veins too great to prevent their removal. In 19 lymph glands carcinoma was present. Out of the 26 patients 12, or 46.1 per cent, showed cancer in the lymph glands removed, or dividing them into groups, we found 8 with cancerous lymph glands out of 18 Group II cases (44.4 per cent) and 4 out of 8 Group III cases (50 per cent). Of special interest is the fact that the two patients operated on in 1930 and now free of recurrence showed cancer in the lymph glands removed, and 5 out of the 11 Group II patients now clinically well showed such cancerous metastasis.

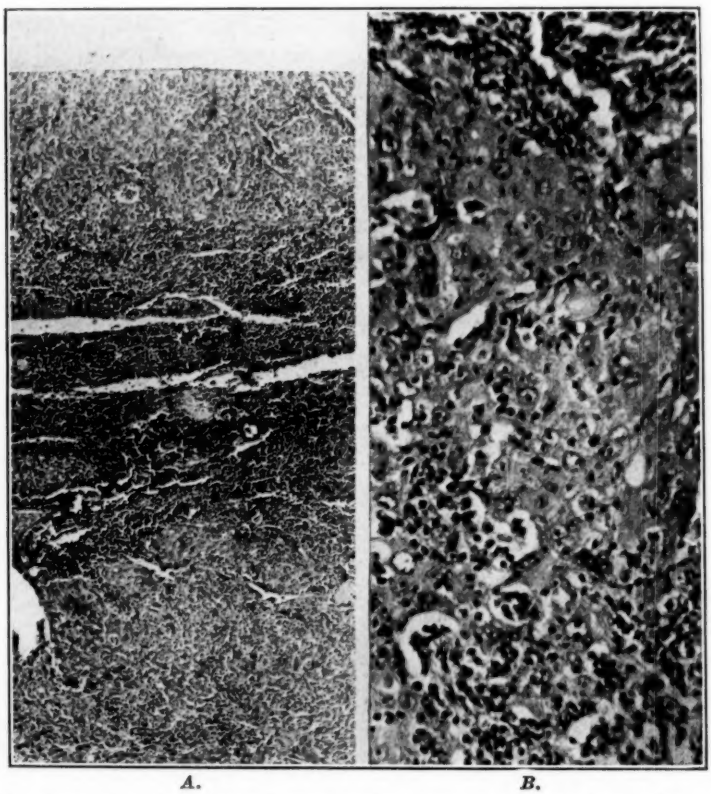
As evidence of the extent and type of metastasis found in these lymph glands, a few photomicrographs have been made. Fig. 5 shows the metastasis in the patient (Case 1) operated in October, 1930, and still free of recurrence. Fig. 6 shows a metastasis apparently of low malignancy (Grade 2) with well-differentiated squamous epithelium. In another section, Fig. 7, we see the histologic picture of a ureteral lymph gland with cancer growing actively and no irradiation effect although 3,600 mg. hr. of radium had been applied to the cervix at a distance of less than 4 cm. from the gland four weeks before its removal. As

an index of the size of some of these cancerous lymph glands, they were photographed with the tubes and ovaries removed (Fig. 8). This pa-



A. *B.*

Fig. 5.—Lymph gland from Case 1 operated October, 1930, still clinically well: *A.* Low power showing cancer nests. *B.* High power of metastasis with well-differentiated epithelium.



A. *B.*

Fig. 6.—Case 3. Lymph gland from patient operated September, 1931, clinically well, showing metastasis with a Grade I malignancy index. *A.* Low power. *B.* High power.

tient, operated on in August, 1932, is still clinically well (April, 1934). Fig. 9 shows a microscopic picture of this gland. The large glands in

Fig. 10 were from a Group III case. An histologic section from another patient operated on three and one-half years ago, clinically well with cancer in lymph gland, is shown in Fig. 11. While I would not at the

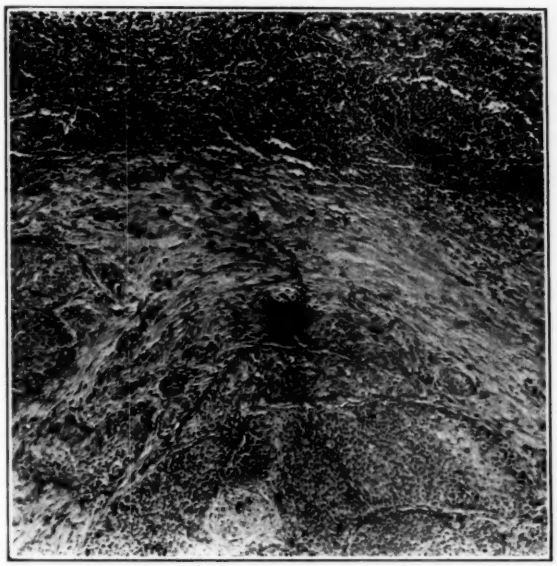


Fig. 7.—Ureteral lymph gland showing actively growing cancer nests, although 3,600 mg. hr. of radium had been applied to the cervix at a distance of 3 or 4 cm. from this gland four weeks previously.

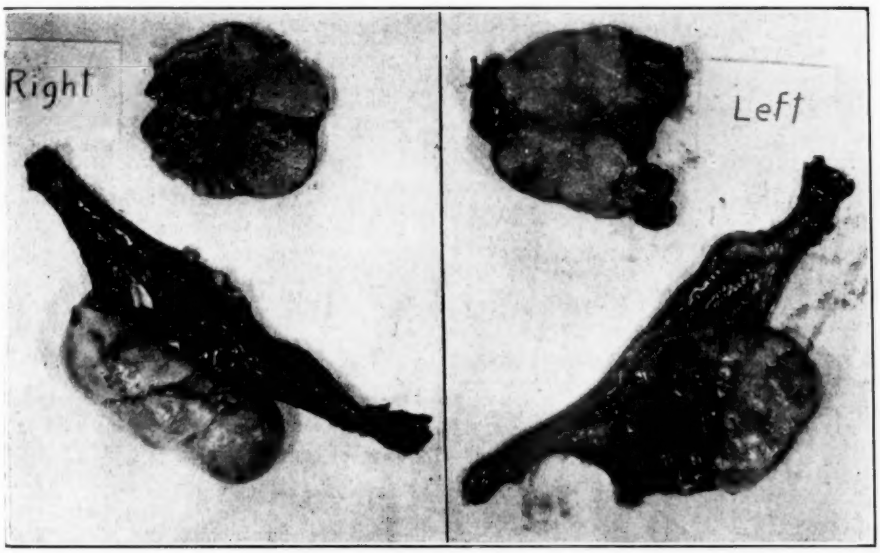


Fig. 8.—Iliac lymph glands cut open to show large cancer metastases and tubes and ovaries removed from same patient to show size. The patient was clinically well two and one-half years later.

present time be willing to make any definite statement, I have had the impression that the grading of the lymph gland metastasis even more

than that of the primary tumor was of some prognostic value, the more malignant showing a higher incidence of recurrence.

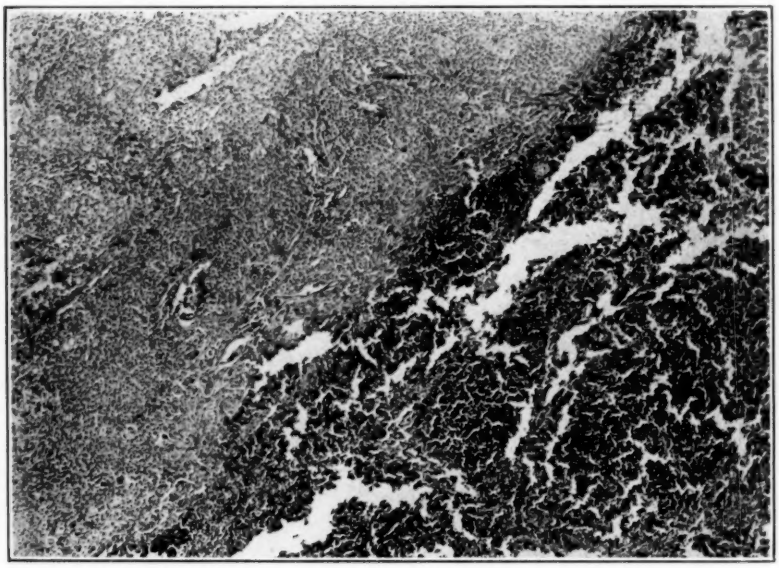


Fig. 9.—Photomicrograph of metastasis from gland in Fig. 8.

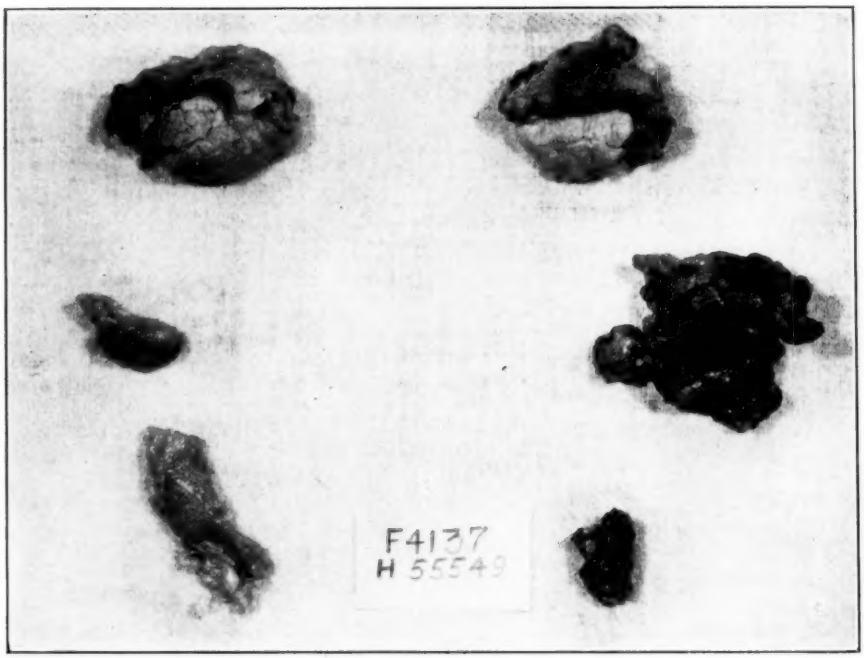


Fig. 10.—Photograph of unusually large iliac and obturator lymph glands with adnexa removed from same patient, who died with recurrence four months later.

I quite concur in the general skepticism regarding the so-called "precancerous hyperplasia" in lymph glands described by the French. On the

other hand, the mere fact that cancer has not been demonstrated in the removed lymph glands does not prove that their removal has been useless. In cancer of the breast and mouth we have ample clinical evidence of the

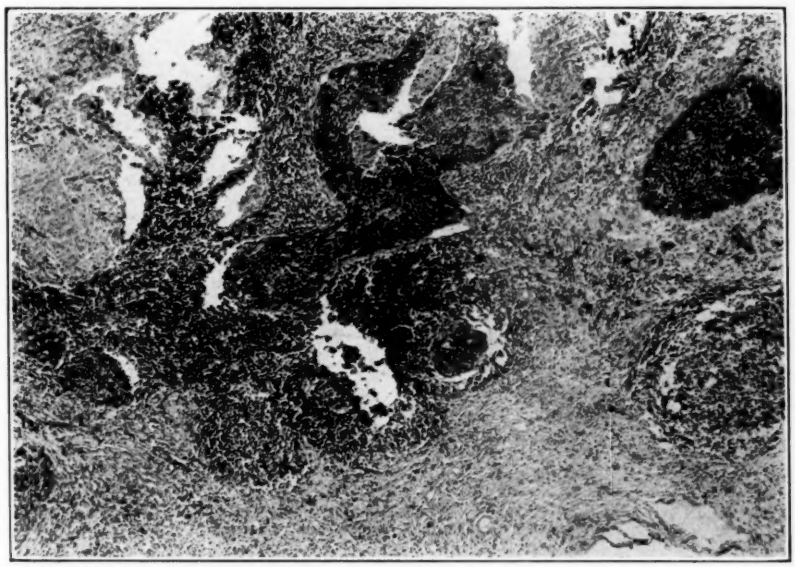


Fig. 11.—Case 2. Lymph gland from patient operated December, 1930, now clinically well, showing a cancer metastasis of intermediate malignancy.

Fig. 12.—Iliac lymph gland with glandular elements resembling uterine epithelium taken from a case of Group III cancer of the cervix. Wertheim considered this epithelium evidence of metastasis. It is more probably an endometrial implant as explained by Sampson. Apparently a condition more often associated with cancer of the cervix.

value of extensive lymph gland removal even if no cancer is found histologically in such glands. Many of the lymph glands in our patients

were hard and large (up to 5 cm. in diameter), and often these glands showed no carcinoma. An interesting finding in one of the iliac glands removed in a squamous carcinoma of the cervix showed extensive simple endometrial-like glands described by Wertheim as possible metastasis but not so interpreted by us (Fig. 12). Sampson considers them possibly to be endometrial implants carried through the lymphatics.

In cases in which a combination of irradiation and lymph gland surgery has been employed as in our plan of treatment, it is, of course, extremely difficult, especially in so small a series as the present one, to arrive at any positive estimate of their relative value. Comparison with the results of others is particularly difficult because of the varying opinion as to definition of groups. It is possible that the results with this method of treatment will not be any better than that now obtained with deep x-ray and radium, yet certain facts are already evidenced that justify a more optimistic opinion.

In the first place we must stress again the experience of cancer therapists who have found that, regardless of the primary site of the tumor, cancer metastases in lymph glands are more difficult of removal by irradiation than by surgery. Next we must bear in mind that in our 26 cases, lymph gland cancer was actually demonstrated in over 45 per cent and probably occurred considerably oftener. The operative procedure if limited to women in good condition with a tumor not too far advanced (Group II) was not attended by any appreciable operative mortality. Finally, it is shown that the results thus far obtained by this method, 11 out of 18 Group II cases clinically well for from one to three and one-half years, point to the possibility of curing a considerable number of these patients even though cancer had already invaded the immediately tributary lymph glands.

I sincerely hope to have persuaded those of you who still feel that surgery is of some value in the treatment of cancer of the cervix to give a trial to this combined method of attack in suitable cases. This procedure is recommended for patients: (1) in good physical condition and not obese; (2) with tumors not markedly radiosensitive; (3) with involvement of the parametria, but not all the way to the pelvic wall; (4) preferably among the younger group of patients.

SUMMARY OF HISTORIES

GROUP II CASES

CASE 1.—S. S., fifty-one years old, para i, bleeding for six months, had a large everting carcinoma of cervix with some thickening of both parametria. Oct. 14, 1930, after cautery destruction of cauliflower mass, abdomen was opened and, after removal of left adnexa and a small subserous myoma, a large lymph gland in left iliac triangle was removed. No glands were found in right iliac region. Eight gold radon seeds of 1½ mc. each were implanted, 2 in left iliac bifurcation and 6 in parametrium and sacrouterine ligaments encircling cervix. On Oct. 26, 1930, 150

mg. radium in brass were implanted in cervix for twenty-two hours. Slight thickening was still palpable around cervix Dec. 23 to 30, 1930, hence 4 gold radon seeds of 1½ mc. were implanted in left parametrium and cervix. Total radium dosage equaled 5,700 mg. hr. Histologic examination showed squamous carcinoma in cervix and large metastasis in left iliac gland. June 16, 1931, patient clinically well, gained in weight from 121½ to 144½ pounds. Mar. 15, 1934, examination showed her clinically well, weight 145 pounds.

CASE 2.—L. S., forty-two years old, para iii, bleeding for four months, showed cervix completely involved with thickened parametria. Dec. 2, 1930, the abdomen was opened, and after removal of both adnexa, a hard gland in left iliac region was removed, 3 × 2 cm. Six seeds of 1½ mc. each were implanted in sacrouterine ligaments and broad ligament. After closing the abdomen, 75 mg. radium were implanted in cervix for twenty-two hours. On Dec. 30, 1930, radium was reapplied to cervix, 75 mg. for twenty-three hours. Good result; patient gained from 115 to 138 pounds in weight by June 8, 1931. There was suspicious thickening of cervix; hence, July 6, 1931, 6 radon seeds were implanted around the cervix and Aug. 11, 1931, another 6 seeds to cervix. Considerable necrosis (overdosage?) resulted. There was marked sclerosis. After a drop in weight to 130½ pounds on Aug. 31, 1931, she gained to 140 pounds by Jan. 21, 1932, when she was clinically well. Condition remained unchanged until Nov. 28, 1933, when a small local recurrence was treated with 6 more radon seeds of 1½ mc. each and completely disappeared. The total radium dosage was 8,275 mg. hr. Histologic examination of iliac lymph gland showed cancer metastasis. Patient was clinically well on examination Mar. 5, 1934, weight 137½ pounds.

CASE 3.—N. F., twenty-two years old, para ii, bleeding for three months, showed entire cervix and almost entire left parametrium involved. On Sept. 8, 1931, both adnexa were removed and a large gland, 5 × 1½ cm., removed from each iliac angle. Nine radon seeds of 1½ mc. each were implanted in sacrouterine and broad ligaments and after closure 80 mg. radium were applied to cervix for twenty hours. There was good regression, but Nov. 3, 1931, 5 radon seeds of 1½ mc. were applied to a nodular thickening in left cervix and parametrium. Patient gained in weight from 134 pounds to 147 pounds by May 16, 1933. Five radon seeds totalling 9 mc. were applied to small local recurrence in vault June 6. Patient was examined Mar. 29, 1934, and found clinically well. Glands showed no carcinoma. Total radium dosage was 4,460 mg. hr.

CASE 4.—F. P., aged fifty-eight years, para iv, symptoms for six months, showed both parametria thickened with slight vaginal extension. From Oct. 27 to Nov. 3, 1931, she received 700 r. units of x-radiation. On Nov. 6, 1931, laparotomy was performed; both adnexa removed; right ureter dilated; and two enlarged glands removed from each side. Eight radon seeds were placed in the sacrouterine ligaments and in the thickened parametrium, close to uterine vessels on right side. Lymph glands in left side show cancer microscopically. On the evening of the sixth postoperative day after a normal course, with temperature of 99.4° F., pulse 90, respiration 20, the patient suddenly gasped for breath and died within half an hour. No autopsy was performed but certainly death was due to embolus. Total dosage (incomplete) was 1,600 mg. hr.

CASE 5.—Mrs. G., aged thiry-two years, para ii, pregnant three months, with bleeding for two months, showed an involvement of entire cervix and some parametrial thickening. On Oct. 24, 1931, 100 mg. radium applied to cervix for thirty-six hours by Dr. S. Abrams. On Nov. 5, 1931, she had a spontaneous abortion. On Dec. 4, 1931, I was called in consultation. At laparotomy both adnexa and 3 iliac

glands were removed. On left side 2 hard enlarged ureteral glands were felt and removed after ligating the uterine vessels. Five radon seeds were implanted into the sacrouterine ligaments and iliac bifurcation. Microscopic examination of ureteral glands showed actively growing cancer (3,600 mg. hr. of radiation four weeks previously applied 3 or 4 cm. distant from these glands). Dec. 21, 1931, 880 r. units of x-radiation were applied. Local recurrence in August, 1932, was treated with diathermy. In December, 1932, chest metastasis was diagnosed. Patient died January, 1933, with recurrence; total dosage was 4,600 mg. hr.

CASE 6.—L. W., forty-two years old, para v, symptoms for nine months, showed involvement of two-thirds of the cervix and one parametrium almost to the wall. On Dec. 11, 1931, both adnexa, right iliac and left ureteral glands were removed. Six gold seeds of 1½ mc. each were implanted in sacrouterine ligament and iliac bifurcation. On Dec. 29, 1931, 100 mg. radium applied to cervix for twenty-two hours. Microscopic examination of lymph glands showed carcinoma. Total radium dosage was 3,400 mg. hr. Patient reported June 1, 1933, feeling well, no recurrence; Mar. 24, 1934, patient was gaining in weight, no recurrence (letter).

CASE 7.—A. C., aged thirty-one years, para iii, symptoms for two months, showed cauliflower carcinoma of cervix with vaginal and slight parametrial involvement. On Dec. 15, 1931, typical large glands removed from both sides; 3 gold seeds of 1½ mc. each were implanted in sacrouterine and bifurcation on each side; and 100 mg. of radium placed in cervix for twenty-two hours. On Jan. 26, 1932, 50 mg. radium were placed in cervix for twenty-four hours. Total radium dosage was 4,600 mg. hr. Patient was clinically well with gain in weight from 168 to 182 pounds on May 31, 1932. She weighed 193½ pounds on Oct. 9, 1933. When examined Mar. 20, 1934, she was clinically well. Cancer metastasis was found microscopically in left iliac gland.

CASE 8.—M. C., fifty-three years old, para ii, symptoms for two months, showed both parametria moderately involved. On Dec. 11, 1931, radium to cervix for a total of 3,150 mg. hr. On Jan. 12, 1932, glands were removed from both sides, definitely carcinomatous on left side. Three radon seeds were placed on each side and 50 mg. radium placed in cervix for twenty-four hours with good immediate result. Patient gained in weight from 185 to 194½ pounds. X-radiation was given prophylactically in October, 1932, and repeated in November, 1932; total amount, 1,205 ma. Probably excessive! Severe hemorrhage with necrosis of cervix was noted Dec. 19, 1932. Rectovaginal and vesicovaginal fistulas developed. Patient died with recurrence Oct. 25, 1933. Total radium dosage was 5,550 mg. hr. plus x-ray. Left iliac lymph gland showed carcinoma.

CASE 9.—M. S., fifty-two years old, colored, para v, symptoms over three months; cervix, upper vagina, and left parametrium were involved with fibroid uterus. On Dec. 7, 1931, 150 mg. radium was placed in cervix for twenty-one hours, or 3,150 mg. hr. On Jan. 19, 1932, removed fibroid fundus of uterus with adnexa for technical reasons. Two large glands on left side and one on right side were removed. Two gold seeds of 1½ mc. were placed in each sacrouterine ligament and 50 mg. radium implanted in cervix for twenty-four hours. Total dosage was 5,150 mg. hr. Immediate result was good. Recurrence was noted Jan. 25, 1933, and patient died May 31, 1933. No cancer was found in lymph glands.

CASE 10.—B. C., fifty-five years old, colored, para ii, complained of bleeding for two months; both parametria were somewhat thickened. On Apr. 21, 1932, lymph gland removal was performed. No radon seeds were available, but 100 mg. of radium were placed in cervix for thirty-six hours. Small recurrence on Nov. 14, 1932, was treated by radium to cervix with dosage of 1,170 mg. hr. Patient died of recurrence June 24, 1933; no cancer was found in lymph glands.

CASE 11.—S. H., thirty-four years old, para iv, complained of symptoms for two years, entire cervix was involved and there was some involvement of both parametria. On Aug. 9, 1932, adnexa were removed, and unusually large, evidently malignant, glands were removed from both iliac triangle (Fig. 8). Smaller obturator glands were also found. Dissection was difficult. Radium and radon seeds were not available on that day. Aug. 27, 1932, radium applied to cervix 150 mg. for twenty-two hours, or 3,300 mg. hr. By Dec. 15, 1933, she had gained 20 pounds and was clinically well. She was examined Mar. 10, 1934, and was found clinically well. Cancer was found in both iliac glands.

CASE 12.—B. L., aged thirty-four years, nulliparous, had symptoms for three months; the cervix was involved with left parametrium thickened. On Nov. 22, 1932, typical lymphadenectomy was performed, and 5 gold radon seeds implanted in sacrouterine and iliac triangle and 85 mg. radium in cervix for twenty-five hours. On Dec. 16, 1932, additional 50 mg. radium to cervix for twenty-four hours, a total radium dosage of 4,375 mg. hr. In December, 1932, x-radiation up to 900 ma. was given. Patient gained in weight from 96½ to 129 pounds and was perfectly well Nov. 28, 1933. Lymph glands show only hyperplasia. A relative reported her to be in good health Apr. 30, 1934.

CASE 13.—B. K., aged forty-two years, para i, complained of symptoms for nine months; cervix and both parametria were partly involved. On Dec. 9, 1932, two iliac glands from right side and one ureteral gland from left side were removed. Five gold seeds were implanted abdominally and 150 mg. of radium placed in cervix for twenty-two hours. Total radium dosage was 4,360 mg. hr. There was temporary improvement X-ray treatment was given in April, 1933 (450 ma.). Colostomy was performed for obstruction on Sept. 29, 1933. Patient died Jan. 1, 1934; no carcinoma in lymph glands.

CASE 14.—A. H., fifty-six years old, para iv, had symptoms for one year, cervix and left parametrium involved extensively. Dec. 20, 1932, received x-radiation totalling 900 ma. On Jan. 31, 1933, typical lymphadenectomy was performed with implantation of 3 gold seeds in each side. Total radium dosage was 4,500 mg. hr. July 21, 1933, she was clinically well, and on Mar. 12, 1934, was gaining in weight, and was clinically well. No cancer was found in the lymphatics.

CASE 15.—E. deW., aged thirty-four years, para i, had symptoms for five months; there was cervical and slight parametrial involvement. Aug. 8, 1933, received 900 ma. of x-ray treatment. On Sept. 8, 1933, typical lymphadenectomy was performed. No radon seeds were available on that day, and 150 mg. of radium were applied to cervix for only fourteen hours by mistake. Hence on Nov. 28, 1933, additional radon seeds were given vaginally into the parametrium for a dosage of 1,200 mg. hr. Total radium dosage was 3,300 mg. hr. On Mar. 16, 1934, she was clinically well, having gained 14 pounds in weight in the previous three months. No cancer was found in glands.

CASE 16.—B. McC., thirty-four years old, para i, complained of symptoms for three months; entire cervix was involved with beginning parametrial thickening. On Nov. 3, 1933, x-radiation up to 900 ma. was given. On Dec. 5, 1933, numerous lymph glands were removed, including right ureteral gland. No radon seeds were available; 115 mg. radium applied to cervix for twenty-eight hours. Small pyometra developed Dec. 29, 1933, but after drainage condition was good. On Mar. 20, 1934, she was found clinically well and gaining in weight. Total radium dosage was 3,230 mg. hr. No cancer was found in lymph glands.

CASE 17.—B. S., aged forty-eight years, para ii, showed left parametrium and cervix involved. Nov. 17, 1933, she received 900 ma. of x-ray. On Dec. 15, 1933, at

laparotomy large adnexal swellings (chronic hydrosalpinx) were found. Typical lymphadenectomy was performed followed by 115 mg. of radium to cervix for twenty-six hours. On Feb. 9, 1934, additional 2,000 mg. hr. of radium were applied to cervix. Total radium dose was 5,000 mg. hr. Cervical necrosis with hemorrhage and probable recurrence was noted on Apr. 1, 1934. No cancer was found in lymph glands.

CASE 18.—V. K., aged twenty-nine years, para ii, had symptoms for two months; there was large involvement of cervix with left-sided parametrial thickening. On Dec. 8, 1933, x-radiation of 900 ma. was given. On Jan. 2, 1934, 115 mg. radium was applied to cervix for twenty-eight and two-thirds hours (3,246 mg. hr.). On Jan. 30, 1934, lymphadenectomy including removal of left ureteral gland and several large iliac glands was performed. On Mar. 2, 1934, 75 mg. of radium were applied for twenty-four hours to cervix. Total radiation was 5,046 mg. hr. plus 900 ma. Immediate result was good. No cancer was found in lymph glands.

GROUP III CASES

CASE 1.—I. F., aged forty years, para ii, complained of symptoms for several months; there was involvement of entire cervix, upper vagina, and both parametria extensively. On Nov. 10, 1931, typical lymph gland removal was performed, with large glands found on each side. Three radon seeds were implanted on each side and 100 mg. of radium placed in cervix for twenty-one and one-half hours. On Dec. 22, 1931, additional radium (1,200 mg. hr.) was applied to cervix. Feb. 2, 1932, x-radiation of 900 ma. was begun, and on Sept. 13, 1932, an additional 700 ma. was given. On Nov. 10, 1932, development of a cervical slough was noted, apparently due to overradiation. She gradually increased in weight from 119 pounds to 133 pounds on May 15, 1933. Total dosage was 4,550 mg. hr. plus 1,600 ma. Ureterovaginal fistula developed Dec. 8, 1932. On March 9, 1934, there was no evidence of carcinoma although fistula persisted with weight increased to 136½ pounds. Lymph glands on both sides showed carcinoma.

CASE 2.—M. G., aged forty-two years, para ii, had symptoms for two years; entire cervix and both parametria were extensively involved. On Jan. 29, 1932, operation was complicated by adhesions and salpingitis. Glands were removed from both sides. Three radon seeds of 1½ mc. each were placed in each side. Fifty milligrams of radium were applied to cervix for twenty-four hours, total radiation of 2,400 mg. hr. Patient died of peritonitis five days after operation. No cancer was found in lymph glands.

CASE 3.—B. H., thirty-two years old, gave a history of symptoms for six months, partial cervix amputation three months before admission; entire right parametrium was involved with infiltration of left side also. On June 29, 1932, 150 mg. of radium were applied to cervix for twenty-seven hours (4,050 mg. hr.). Results were fairly favorable; hence on Sept. 13, 1932, laparotomy and removal of double-sided infected adnexa with small pus sac were performed. Only one iliac lymph gland was found. Five radon seeds were implanted. Postoperative course was stormy and the incision was reopened for localized peritonitis. Colostomy was performed Dec. 14, 1932, for partial obstruction. Radiation dose totalled 5,250 mg. hr. Patient died of recurrence in May, 1933. Lymph gland showed no carcinoma.

CASE 4.—A. O., Eskimo Indian, thirty-three years old, para vii, had symptoms for several months. Entire cervix and both parametria were extensively thickened. On Sept. 27, 1932, 150 mg. radium were applied to cervix for twenty-two hours. On Oct. 18, 1932, lymphadenectomy was performed; glands were found only on right side; 3 radon seeds were implanted on each side. On Nov. 11, 1932, x-radiation of 900 ma. was given. Only temporary improvement resulted. Recurrence was noted

Mar. 10, 1933. Patient died July 9, 1933. Total radiation dosage was 4,500 mg. hr. plus 900 ma. Iliac lymph glands showed cancer.

CASE 5.—L. B., colored nullipara, aged twenty-five years, complained of symptoms for three months; slight infiltration of parametria was noted at first visit July 3, 1932; she did not return for treatment until Nov. 4, 1932, when both parametria were extensively infiltrated; 150 mg. radium were applied to cervix for twenty hours. On Jan. 27, 1933, lymphadenectomy was performed, and 4 radon seeds implanted in sacrouterine ligaments. Apr. 7, 1933, x-radiation of 800 ma. Recurrence July 3, 1933. Patient died Oct. 30, 1933. Total dosage of radium was 3,800 plus 800 ma. No cancer was found in glands.

CASE 6.—M. L., aged forty-four years, para vii, had a history of symptoms for eleven months; there was an inverting growth of the cervix with both parametria markedly thickened. On Sept. 19, 1932, x-radiation of 800 ma. was begun. On Oct. 13, 1933, 150 mg. radium were applied to cervix for twenty-six and two-thirds hours. On Nov. 21, 1933, laparotomy was performed, and very numerous large lymph glands were found with one ureteral node firmly attached to right ureter. On left side was a similar adherent ureteral lymph gland. Four radon seeds were placed in these glands. Radium was placed in cervix (50 mg. for twenty-four hours). Postoperative course was stormy, and patient died Feb. 28, 1934, probably with recurrence. Carcinoma was found in glands of both sides.

CASE 7.—C. C., aged forty-three years, para vii, complained of symptoms for six months; both parametria and cervix were extensively thickened. On Nov. 28, 1933, 900 ma. of x-radiation were begun. Operation was difficult with many old inflammatory adhesions (Jan. 5, 1934). Left ureteral gland was too adherent to remove. Eight radon seeds of 2.1 mc. each were placed in sacrouterine ligaments and iliac bifurcation area, followed by cervical application of 115 mg. radium for twenty hours. Postoperative course was stormy, with pelvic peritonitis and death four weeks later on Feb. 1, 1934. Autopsy showed generalized peritonitis, but no carcinoma was found in glands at autopsy. No cancer was found in glands that were removed. Total radiation dosage was 4,534 mg. hr. plus 900 ma.

CASE 8.—T. V., aged forty-seven years, para iii, had a history of symptoms for six months; there was involvement of vagina and left parametrium almost to pelvic wall. On Dec. 12, 1933, x-radiation of 900 ma. On January 9, 1934, lymphadenectomy was performed without difficulty. Eleven gold seeds of 1.1 mc. each were implanted in sacrouterine ligaments and pelvic connective tissue, and 75 mg. of radium were put in cervix for twenty-six and two-thirds hours. Total dosage equaled 3,515 mg. hr. Patient developed a temperature that reached 108° F. forty-eight hours later when she died. Autopsy showed no peritonitis but marked changes in liver, parenchymatous degeneration, and extensive fatty infiltration indicating a seriously damaged liver function before operation. Many large lymph nodes were found about aorta. None of the glands removed at operation or autopsy showed carcinoma.

REFERENCES

Baisch, K.: Arch. f. Gynäk. **75:** 273, 1905. *Brunet:* Ztschr. f. Geburtsh. u. Gynäk. **56:** 632, 1905. *Gellhorn:* Surg. Gynec. Obst. **58:** 879, 1934. *Kermauner:* Halban-Seitz, Pathol. u. Biol. d. Weibes **5:** 843, 1927. *Kundrat:* Arch. f. Gynäk. **69:** 355, 1903. *Lahm:* Halban-Seitz, Pathol. u. Biol. d. Weibes **4:** 701, 1927. *Leitch:* Cited by Lynch. *Lynch:* Pelvic Neoplasms, 1922, p. 221. *Mackenrodt:* Monatschr. f. Geburtsh. u. Gynäk. **19:** Part 6, 1904. *Pankow:* In Veit-Stoeckel Handbuch d. Gynaekologie **6:** Part 2, 543-595. *Philipp:* Strahlentherapie **43:** 109, 1932. *Schauta:* Monatschr. f. Geburtsh. u. Gynäk. **19:** Part 4, 1904. *Schottlaender and Kermauner:* Das Uterus-carcinom, 1912, pp. 602-721.

3720 WASHINGTON AVENUE

THE NATURE OF OVARY-STIMULATING HORMONES*

C. F. Fluhmann, M.D., C.M., San Francisco, Calif.

(From the Department of Obstetrics and Gynecology, Stanford University School of Medicine)

SINCE the discovery by Aschheim and Zondek in 1928 that the blood and urine of pregnant women contain large amounts of some hormone which has the property of inducing changes in the ovaries of laboratory animals, further studies have revealed the existence of similar substances under many conditions. At first it was maintained that all these hormones originated in the anterior lobe of the pituitary gland, and although this belief is still held, especially by German investigators, there is a widespread skepticism regarding this explanation, and it seems more likely that we are in fact dealing with very different substances. It is of especial importance to determine the exact nature of these hormones in order to interpret the true significance of their occurrence in various pathologic conditions and to develop a sound basis for their employment as therapeutic agents. The present report deals with an analysis of ovary-stimulating factors found in the human anterior pituitary gland, in the blood and urine of women during gestation, after castration or the menopause, and associated with chorioepithelioma, and in the urine of men with teratoma of the testis.

Although there may be several ways of approaching this problem, a very useful method is to compare the biologic effects of the hormones in different laboratory animals in order to determine their degree of similarity. Such studies have been conducted by a number of workers during the past few years, and in a recent review (Fluhmann[1]) I was able to point out ten different procedures which may be used for this purpose. In the present investigation, I have relied chiefly upon three tests. First, a careful comparison was made of the finer histologic changes resulting in the ovaries of immature white rats after the injection of extracts by a standardized method. Second, an analysis was made of the effect of various extracts on ovarian weight by comparing the percentage of increase found in a group of immature rats given a known dose of the hormone over a period of five days, with that produced in a control series by the same dose administered for ten days.[2] The third test employed was a study of the histologic changes induced

*Supported in part by the Rockefeller Fluid Research Fund of Stanford University School of Medicine. My thanks are due to Dr. D. A. Wood and members of the Department of Pathology for the human anterior pituitary glands from autopsy material, and to Mr. John J. Kan and Mr. Pierre Lassègues for their technical assistance.

by various preparations in the atrophied ovaries of hypophysectomized mature and immature rats.

The technical procedures employed in the Stanford Gynecological Laboratory and details regarding the animals, their age at maturity, the method of estimating organ weights and their percentage of increases, and the standardized way in which the extracts are administered, have been fully described in a number of previous communications.[3, 4, 5, 6, 7] The preparation of ovary-stimulating extracts from blood of pregnant women has also been given.[3, 6] This method is based on the work of Wallen-Lawrence and Van Dyke,[8] and depends on an alcohol precipitation of citrated blood, extraction of the precipitate with a sodium-acetate-acetic acid buffer, pH 4.2 to 4.5, and reprecipitation of the active material with 95 per cent ethyl alcohol. The human anterior lobe extracts were prepared from autopsy material obtained from patients of both sexes and of all ages. The fresh glands were cut into small fragments and kept in acetone for several days or weeks, and were finally dried *in vacuo* at room temperature. They were then ground up, and the resulting powder extracted in the same way as that used for making extracts from blood of pregnant women. The specimens of urine were either injected directly into the rats, or they were concentrated by precipitation with 95 per cent alcohol, as originally described by Zondek.[9]

The extracts which were employed are crude chemical preparations, but they all showed a high degree of gonad-stimulating properties. In view of recent developments pointing to the close association of several different hormones of the anterior lobe, it was of importance to determine the presence or absence of these various factors and to see if they may alter the action of the gonadal hormone. In a recent extensive study[10] it was found that the pregnancy-blood extracts depressed thyroid function when first administered, while the anterior lobe preparations made from sheep, rat, or human sources produced a marked increase in the basal metabolism and when given in sufficient doses even caused a hyperplasia of the thyroid gland. On the other hand, it was clearly shown that the presence of the thyroid-stimulating factor did not interfere with any characteristic histologic modification of the ovaries in the tests employed in the present study. The amount of thyroid-stimulating hormone found in the extracts prepared from human glands was also much less than in those made from sheep or rat pituitaries. The experiments conducted with hypophysectomized rats suggest that if growth or adrenotropic hormones were present in the extracts they must have been very small in amount. No information as yet has been secured regarding the possible prolactin content of these preparations.

The hypophysectomized rats used in these studies were obtained through the dexterity of my associate, Dr. P. E. Hoffmann. The operation was performed by the parapharyngeal approach originally

devised by P. E. Smith[11] but with certain modifications introduced by Pencharz and Long.[12] The complete removal of the hypophysis was determined in three ways: (1) by failure of the rats to increase in weight for from sixteen to twenty-four days after hypophysectomy; (2) by removing one ovary at the beginning of each experiment to determine histologically if posthypophysectomy atrophy had occurred; and (3) by a careful examination of the skull at autopsy.

OVARY-STIMULATING EXTRACTS FROM HUMAN ANTERIOR PITUITARY GLANDS AND BLOOD OF PREGNANT WOMEN

During the past two years I have conducted an extensive comparative study of the biologic characteristics of extracts prepared by the same

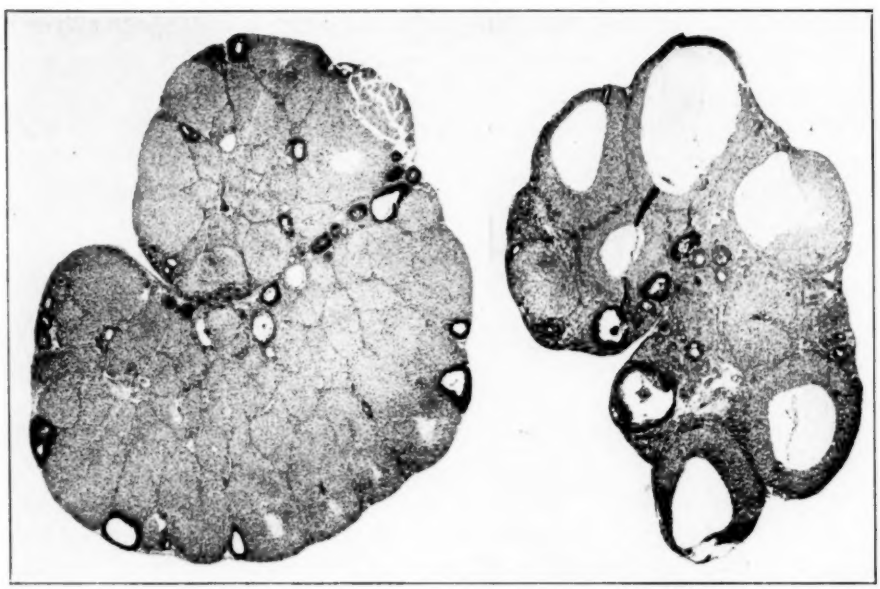


Fig. 1. Fig. 2.

Fig. 1.—Ovary of an immature rat injected with a human anterior pituitary extract.

Fig. 2.—Ovary of an immature rat given an ovary-stimulating extract made from blood of pregnant women.

process from sheep anterior pituitary material and blood of pregnant women. These preparations were given in various ways to many hundreds of immature white rats, and it was shown that, when a standardized method of administration is employed, there is a striking difference in the histologic picture induced by the different extracts in the ovaries of the test animals. The method finally adopted was to give each rat two injections daily of 0.25 c.c. of the various dilutions of the respective extracts and to allow an interval of approximately 120 hours from the time of the first and thirty-six hours from the time of the last injection to elapse before autopsy.[6] Any deviation from this scheme may produce radical differences in the resulting picture in the

ovaries, and it is also advisable to give doses sufficient to produce increases of from 100 to 500 per cent in the weight of the ovaries.

On repeating this work with extracts prepared from human pituitary glands, it was found that these preparations behaved in essentially the same manner as those made from sheep material. The ovaries of the rats in 120 hours showed the presence of large numbers of small, closely packed corpora lutea (with or without imprisoned ova), interspersed with many follicles undergoing chromatolytic degeneration (Fig. 1). It would seem, therefore, that the administration of anterior lobe hormone causes a sudden development of many follicles, which then undergo luteinization. This process is well advanced in forty-eight hours and is apparently completed in ninety-six hours, when the injections are discontinued and the follicles which failed to luteinize undergo degeneration. If very large doses of the human anterior pituitary extracts are given, it is possible to obtain ovaries which show no atretic follicles but solely large numbers of small corpora.

On the other hand, the extracts made from blood of pregnant women behaved in a very different way, suggesting that their effect is produced by a different mechanism. In 120 hours the ovaries did not present the picture of large numbers of small corpora with atretic follicles, but there were, instead, a few large corpora lutea (with or without imprisoned ova), large developing graafian follicles, and follicles which were undergoing luteinization and appeared as "lutein cysts" (Fig. 2). There were but few, if any, atretic follicles. It is of interest that this histologic picture could be seen as early as from forty-eight to sixty hours after the first injection and was constantly found even if the administration of the extract was continued for twenty days.

There is thus a fundamental difference in the effects induced in the immature rat ovary by the ovary-stimulating hormone of pregnant women and the effects brought about by anterior lobe factors. This difference, moreover, cannot be explained on the basis of dosage since it may appear at all dose levels which produce a definite increase in ovarian weight. The first observation relating to these differences in the histologic picture in the ovaries seems to have been made by Engle[13] and Orban and Watrin,[14] while the results of a recent extensive study by Hamburger[15] conform essentially with those given in the preceding paragraph.

In keeping with the variations in the histologic appearance of the ovaries is a difference in their response with increases in weight to the administration of the *same total dose* of an extract over various periods of time.[2] In performing this test, from 8 to 18 rats were divided into two groups, distributing litter mates evenly in each section. Group A was then given an injection of 0.25 c.c. of an extract twice daily for five days, when the animals were killed and the average percentage of in-

crease in ovarian weight determined. Group B received two injections daily of 0.25 c.c. of the same extract diluted with an equal amount of distilled water or buffer solution for a period of ten days, and the average percentage of increase in ovarian weight was then estimated. Each group of rats thus received the same total dose of the extract, but in one case it was given for five days and in the other for ten days.

A significant difference was found between the two hormones. In the case of the anterior lobe extracts, whether made from human, sheep, or

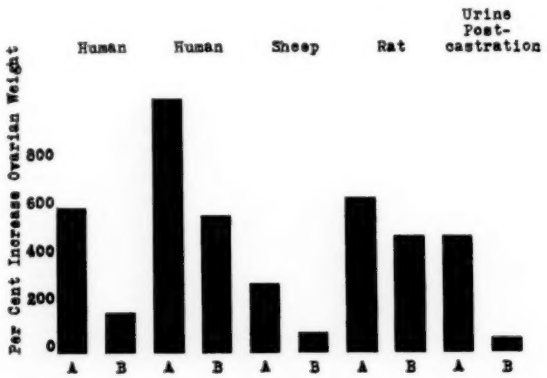


Fig. 3.—Anterior pituitary group. Diagram illustrating the effect on the ovarian weight of immature rats of injecting a known total dose of various ovary-stimulating extracts for different periods of time. The columns "A" represent the average percentage of increases obtained in five days; in this group they are greater than columns "B," which show the increase resulting from the administration of the same total doses over periods of ten days.

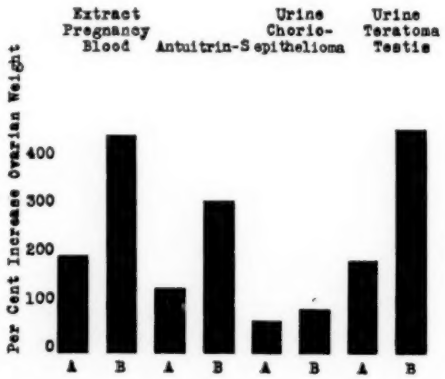


Fig. 4.—"Chorionic hormone" group. Diagram illustrating the effect on the ovarian weight of immature rats of injecting a known total dose of various ovary-stimulating extracts for different periods of time. The columns "A" represent the average percentage of increases obtained in five days; in this group they are smaller than columns "B," which shows the increases resulting from the administration of the same total doses over periods of ten days.

rat material, the ovaries of the rats receiving the extract for five days were always larger than those of the animals injected for ten days (Fig. 3). For instance, a group of 9 rats was given a human pituitary extract for five days and showed an average increase of 600 per cent in ovarian weight. Nine control rats, receiving the same total dose for ten days,

showed an increase in ovarian weight of only 162 per cent. On the other hand, the reverse occurred when the ovary-stimulating hormone of pregnancy was used, the animals injected for the longer period having the heavier ovaries (Fig. 4). For example, 5 rats injected for five days with a pregnancy-blood extract gave an average increase of 200 per cent in ovarian weight, but when the same total dose was given to a group of 5 rats for ten days, the average increase was 450 per cent. The same result was obtained with other similar prolan preparations, such as antuitrin-S (Parke, Davis & Company) and follutein (E. R. Squibb and Sons).

Of the various tests developed to compare the biologic characteristics of ovary-stimulating hormones, the injection of these substances into hypophysectomized rats is probably the most valuable. Smith[11] unquestionably demonstrated that atrophic changes soon occur in the ovaries of rats after this operation (Figs. 5 and 6). Although primordial follicles continue to develop, and corpora lutea persist for many months without showing histologic evidence of degeneration, there is a rapid

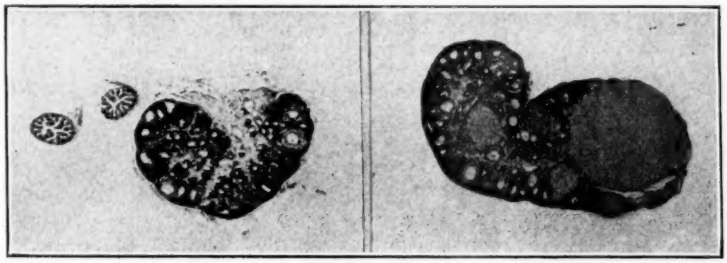


Fig. 5. Fig. 6.

Fig. 5.—Atrophy of the ovary of an immature rat following a total hypophysectomy.

Fig. 6.—Atrophy of the ovary of a mature rat following a total hypophysectomy.

marked regression in the size of the ovaries; atresia sets in very soon in all medium-sized and large follicles; and there is a characteristic atrophy of the interstitial tissue (Selye, Collip, and Thomson[16]). The implantation of fresh anterior lobe material (Smith[11]) or the administration of suitable extracts (Collip and his coworkers[17]) to hypophysectomized rats results in a few days in the restoration of the ovaries to almost normal structure and activity. This is evidenced by the appearance of estrous changes in the vagina, by growth of the uterus, and by development of graafian follicles with subsequent corpus luteum formation in the ovaries.

The effect of a human anterior lobe extract was studied in 10 hypophysectomized rats, of which 8 were sexually immature and 2 mature at the time of operation. The experiments were completed in from four and one-half to nine days, with uniform results. The vaginal introitus was found established and a smear of cornified cells was obtained on the fourth or fifth day. At autopsy the uterus and ovaries were found

markedly enlarged. The histologic changes in the ovaries were striking and unmistakable. In the first place, there was evidence of an extensive hypertrophy and overgrowth of the interstitial tissue, with a complete disappearance of the atrophic cells described by Selye, Collip, and Thomson.[16] In addition, follicle growth as well as luteinization were stimulated so that graafian follicles in various stages of development, lutein cysts, and many corpora lutea were seen (Fig. 7).

On the other hand, the changes elicited by pregnancy-blood extracts in 5 hypophysectomized female rats were different from those produced by the pituitary hormone, and corresponded essentially with those already described as resulting from various prolan preparations by Noguchi,[18] Collip and his coworkers,[19] and Smith and Leonard.[20] The vagina within a few days gave a cornified smear which, in two instances,

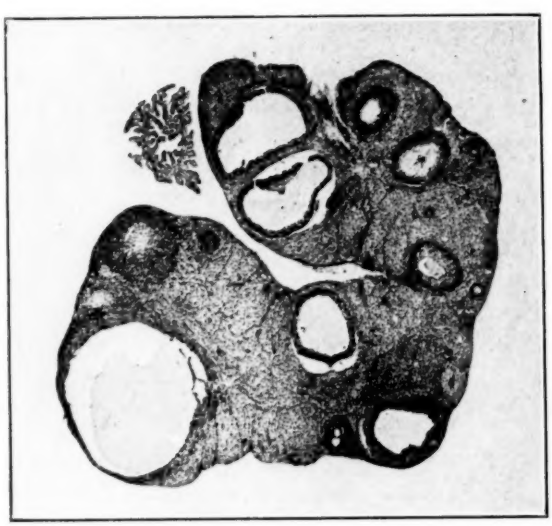


Fig. 7.—Ovary of a hypophysectomized rat (immature) injected twice daily for four and one-half days with a human anterior pituitary extract.

persisted for over two weeks while the administration of the hormone was continued. The ovaries increased in size but not to the same extent as with anterior lobe extracts, and histologically they showed the marked hypertrophy of interstitial tissue which was previously noted. There was, however, a significant difference in that no evidence of follicle growth was seen, although, in agreement with Smith and Leonard,[20] an occasional lutein cyst or recent corpus luteum was observed.

It is thus seen that the three tests employed in this study served to demonstrate clear-cut differences in the biologic characteristics of ovary-stimulating extracts made from human anterior pituitary glands and from blood of pregnant women. First, in normal immature white rats the pituitary preparations caused a rapid growth of many follicles with the appearance in five days of numerous corpora lutea and atretic follicles,

whereas pregnancy-blood extracts incited a slower process with the appearance in five days of large developing follicles, lutein cysts, and corpora lutea. Second, when a total fixed dose of anterior lobe extract was given over a period of five days it resulted in a much greater increase in ovarian weight than when the same dose was spread out over ten days, while with the pregnancy-blood extract the "time factor" was of importance and the animals injected for ten days had the larger ovaries. And finally, a distinct difference was found when these preparations were given to hypophysectomized rats. The anterior lobe extract produced a marked increase in the weight of the ovaries due to a hypertrophy of interstitial tissue and the production of many graafian follicles with their subsequent luteinization. On the other hand, the administration of pregnancy-blood extract resulted in a hypertrophy of interstitial tissue, but with only the sporadic appearance of an occasional lutein cyst or recent corpus luteum.

OVARY-STIMULATING HORMONE IN THE BLOOD AND URINE AFTER CASTRATION

In 1929, I was able to demonstrate the presence of an ovary-stimulating substance in the blood of women after castration, in certain cases of amenorrhea, and in the postclimacteric period (Fluhmann[21, 22, 23]). These results were confirmed by Zondek[24] the following year, who also found this hormone in large quantities in the urine of such patients. He[25] likewise claimed that this factor occurs in the urine of women with various carcinomas of the pelvic organs. In my series, the only positive findings in the blood were in carcinomatous patients who had either passed the menopause or who, in the course of their treatment, had been castrated with large doses of radium or x-rays, and Frank,[26] Hamburger,[15] and others have been unable to confirm Zondek's work in this regard.

In the present investigation, the extracts were prepared from the urine of women who were past the menopause and under treatment for cancer of the vulva or of the cervix uteri.

The histologic study of the ovaries of immature white rats injected as described before, gave results which are closely related to those found with the anterior lobe extracts. There was an extensive development of many graafian follicles, but in contradistinction to the pituitary extract this hormone did not produce any extensive luteinization and usually only a few or no corpora lutea or lutein cysts were seen (Fig. 8).

The "five-and-ten-day" test was conducted three times with this particular hormone, and in each case the results were the same as the results obtained with anterior lobe extracts (Fig. 3). For instance, the injection of 4 rats twice daily for five days with 0.5 c.c. of extract P12 produced an average increase in ovarian weight of 482 per cent. When

the same total dose was given for ten days, the ovaries showed an increase of only 50 per cent.

The effect of this "postcastration hormone" in hypophysectomized rats has not as yet been studied thoroughly in this laboratory. However, in 2 rats which were successfully injected, there was an early development of graafian follicles, and it is also of interest that there was no evident repair of the atrophic changes in the interstitial tissue (Fig. 9). These results seem to confirm those of Leonard and Smith,[27] who reported an extensive follicle growth following the injection of a similar extract in hypophysectomized rats.

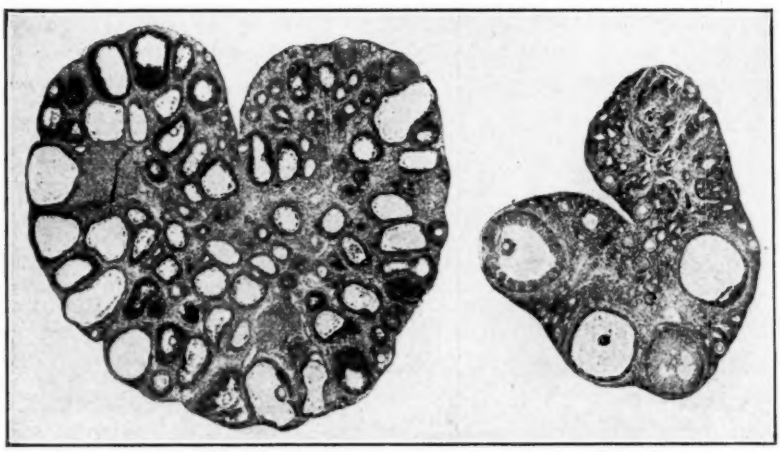


Fig. 8. Fig. 9.

Fig. 8.—Ovary of a normal immature rat given an extract made from the urine of a woman past the menopause.

Fig. 9.—Ovary of a hypophysectomized rat (immature) injected for six days with an extract made from the urine of a woman past the menopause.

URINE EXTRACT FROM A PATIENT WITH CHORIOEPITHELIOMA UTERI

The discovery of Rössler[28] in 1929 that patients with hydatidiform mole or chorioepithelioma uteri may give a positive Aschheim-Zondek reaction has proved to be a valuable clinical observation. Owing to the association of these tumors with gestation, it has been assumed that the ovary-stimulating hormone found in these cases is identical with that occurring during pregnancy, but, so far as I know, no biologic tests have been performed previously to determine the exact nature of this substance.

The urine examined in this study was obtained from a patient under the care of Drs. Reginald Knight Smith and T. Henshaw Kelly of San Francisco. She was a young woman, twenty-nine years old, gravida iii, para i, who developed a chorioepithelioma uteri following a hydatidiform mole. A number of specimens were examined over a period of one month before her death, and in each instance an ovary-stimulating hormone was demonstrated, although the amount present was less than

usually seen in a normal pregnancy. This is of interest as the tumor histologically was composed of small cells with little or no syncytium. The autopsy was performed by Dr. A. M. Moody, who found a tremendous extension of the tumor in the pelvis, with widespread metastases in the liver and in the lungs.

The three tests showed that this hormone is comparable to that found during pregnancy and did not show the characteristics attributed to anterior lobe extracts. The histologic changes were studied in the ovaries of over 25 rats. The "five-and-ten-day" test showed an average increase of 63 per cent in the ovarian weight of 5 rats after five days, and an increase of 90 per cent in 5 rats after ten days, when an extract of the urine was used (Fig. 4). The administration of the untreated urine failed to produce any changes in the ovaries of 2 hypophysectomized rats, but a concentrated extract induced an extensive hypertrophy and hyperplasia of the interstitial tissue, without follicle growth, in four other instances (Figs. 10).

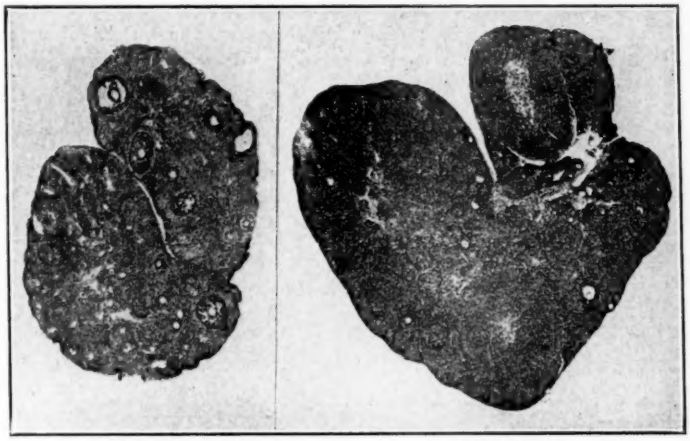


Fig. 10. Fig. 11.

Fig. 10.—Ovary of a hypophysectomized rat (immature) injected for five days with an extract of urine from a patient with a chorioepithelioma uteri with matastases.

Fig. 11.—Ovary of a hypophysectomized rat (mature) injected for ten days with an extract of urine from a patient with a teratoma testis with metastases.

URINE FROM A CASE OF TERATOMA TESTIS

Although the work of Zondek,[29] Ferguson,[30] and others has drawn attention to the occurrence of a gonad-stimulating hormone in the urine of men with various testicular tumors, there is as yet but little information available regarding the biologic properties of this substance.

Evans and his coworkers[31] report that in a case of embryonal carcinoma of the testis with generalized metastases they found a gonad-stimulating factor with characteristics of both the pituitary hormone and that found in women during gestation. In 5 men with testicular tumors and 1 woman with a teratoma of the ovary, Hamburger[15] found a hormone which produced the same histologic picture in the ovaries of immature mice as that resulting from the injection of urine from pregnant women. In a seventh case, a man with an embryoma testis, he obtained results which suggested properties of both types of hormones, as in Evans' patient. Since the patient had been castrated as a consequence of radium therapy, he believed that he was dealing with a mixture of two hormones, one due to the presence of the tumor and the other, a postcastration effect.

I have, as yet, examined only one specimen from this type of case. The patient was thirty-four years old with a teratoma of the testis with metastases for which he was under the care of Dr. J. R. Dillon, of the department of urology.

A twenty-four-hour specimen of urine, obtained on two different occasions, contained about 2,500 rat units of a gonad-stimulating hormone per liter. The histologic picture in the ovaries of over 20 rats injected with the urine or with an extract corresponded to that induced by the pregnancy-blood preparation, and showed corpora lutea, lutein cysts, and developing follicles. The "five-and-ten-day" test was performed twice, and both times the ten-day animals presented a greater increase in ovarian weight (Fig. 4). For instance, in one test the ovaries of 5 rats injected for five days gave an average increase of 190 per cent, while the ovaries of 5 animals receiving the same total dose over a period of ten days had an average increase of 460 per cent. Three hypophysectomized rats were used in testing this specimen, one animal being given daily injections of the untreated urine for one week, while 2 were injected for ten days with a concentrated extract. In the 3 animals the ovaries failed to show evidence of marked follicle growth, and there was a tremendous development of interstitial tissue (Fig. 11).

The gonad-stimulating hormone found in the urine of a man with a teratoma testis was thus found to have the same biologic characteristics as the substance which occurs in the urine of pregnant women.

DISCUSSION

The experimental evidence presented in this paper indicates that the ovary-stimulating hormones which were studied may be divided into two categories. In keeping with the work of Hamburger,[15] the first group may be considered as the "pituitary hormone"; it includes the extracts prepared from anterior lobe material as well as the substance obtained from the blood or urine of women after castration or in the postclimacteric period. The second category, the "chorionic hormone," is made up of material obtained from the blood or urine of women during gestation or associated with hydatidiform mole or chorioepithelioma, and from a case of teratoma testis.

The explanation originally advanced by Aschheim for this division is that all such hormones are of anterior lobe origin but are composed of two pituitary factors. The first is concerned with follicle growth, and the second, with luteinization. The coexistence of these two substances in various proportions would therefore account for any difference in the biologic effect produced by various extracts.

There are many reasons for believing that the anterior pituitary gland produces more than one hormone which affects the sex organs of experimental animals. The work of Hisaw and his collaborators in preparing pituitary extracts with pure follicle-stimulating properties is very impressive. It is unfortunate that other investigators have as yet failed to corroborate these studies, but it is possible to obtain from the urine of women after castration or after the menopause a substance which

stimulates the growth of graafian follicles and produces little or no luteinization.

The problem that now arises is to determine whether the "chorionic hormone" represents a new element, or merely an isolated "luteinization hormone" of the anterior pituitary gland. It is possible that the question must remain unanswered for the present and await further chemical purification of extracts. However, if it is maintained that the anterior lobe actually manufactures this substance, it becomes necessary to advance an explanation for the mechanism by which this gland becomes stimulated during pregnancy or in the presence of certain tumors. This would apparently require the formation of some hitherto unknown hormone. In addition, the anterior lobe enlarges as a result of cessation of gonadal function and an excess of ovary-stimulating hormone appears, but as I have shown in this study, this substance is a very different one from that occurring in pregnant women. And finally, the study of the biologic characteristics of the "chorionic hormone" by Collip and his collaborators, Evans and his associates, Engle, Smith, Philipp, Leonard, Riddle, Schochaert, Hamburger, Fluhmann, and others, strongly supports the conception that it is a new substance produced by the growth of certain embryonal tissues.

It seems wise to accept, at least for the present, the theory that the "chorionic ovary-stimulating hormone" is a factor which is associated with the development of the placenta and certain embryonal tumors, while the one resulting from the cessation of ovarian or testicular activity is a true "anterior pituitary hormone."

The place of the "chorionic hormone" in the physiology of the female pelvic organs during pregnancy is one of vital importance. Although in our state of incomplete knowledge any theory must be considered as pure conjecture, it is interesting to speculate as to its possible function.

The modern study of menstruation is based on an attempt to explain the mechanism of this process by an interaction of various hormones (Corner,[32] Fluhmann[33]). "The sex hormone of the anterior hypophysis stimulates a follicle to develop. As this structure matures, it produces estrin, which in turn causes the endometrium to grow. After full development of the graafian follicle, ovulation takes place, the ovum descends down the fallopian tube to the uterus, and a corpus luteum is formed in the ovary. From now on, there is not only the production of 'progestin,' which controls the development of the characteristic premenstrual changes in the endometrium, but estrin is formed in much greater amounts than before. This estrin production causes a progressive inhibition of the anterior lobe, so that the amount of ovary-stimulating hormone available gradually diminishes. Finally, estrin reaches its peak and correspondingly the amount of anterior lobe sex hormone diminishes to a point insufficient to maintain the corpus luteum. This

structure undergoes degeneration, which results in a cessation of estrin and progestin production and thus a breaking-down of the endometrium (menstruation). The absence of estrin now releases the inhibition of the anterior pituitary gland, which again puts out its sex hormone to stimulate the development of a follicle for the next cycle'' (Fluhmann[33]).

A careful analysis of the various steps outlined in this theory demonstrates at once the difficulty of applying it to the events associated with the onset of pregnancy. With the early development of the ovum it is necessary that the corpus luteum persist. This is seemingly impossible without the prolonged stimulation of the anterior lobe, and this does not occur according to the theory because the large amounts of estrin present act as inhibitors of pituitary function.

Among the possibilities which must be considered at this stage is one which assumes that the ''chorionic hormone,'' produced very early by the developing ovum is the factor that bridges the gap. In other words, the chorionic factor, in the absence of the anterior pituitary sex hormone and in the presence of large amounts of estrin, acts to prolong the life of the corpus luteum which is then able to further the endometrial changes required by the young embryo.

The work of Hartmann has rightly shown the fallacy of the ''primacy of the ovum'' theory in regard to the occurrence of menstruation in normal individuals. It seems justifiable, however, to consider seriously the ''primacy of the ovum'' as regards the initiation of that long series of changes necessary for the successful continuation of a pregnancy in the human. In this, it is possible that the ''chorionic ovary-stimulating hormone,'' by acting to prevent the premature disintegration of the corpus luteum, acts as the messenger of the ovum.

SUMMARY

A comparison was made of biologic characteristics of a number of gonad-stimulating hormones. Three tests were used, and consisted of (1) an analysis of the histologic changes induced in the ovaries of immature rats, (2) a comparison of the effect on ovarian weight of a known total dose of an extract given over periods of five and ten days, and (3) a study of the histologic modifications elicited in the ovaries of hypophysectomized rats.

It was found that the extracts could be divided into two main categories: First, the ''anterior pituitary group'' included preparations made from human hypophysial material and urine of women in the postclimacteric period. Second, the ''chorionic hormone group,'' which included extracts prepared from the blood or urine of normal pregnant women, the urine of one patient with a chorioepithelioma uteri, and the urine of one man with a teratoma testis.

The possible rôle of the "chorionic ovary-stimulating hormone" in the physiology of gestation in the human, is discussed.

REFERENCES

(1) *Fluhmann, C. F.:* Am. J. Obst. & Gynec. **26:** 764, 1933. (2) *Idem:* Proc. Soc. Exper. Biol. & Med. **30:** 1014, 1933. (3) *Idem:* Ibid. **29:** 1193, 1932. (4) *Idem:* Ibid. **30:** 147, 1932. (5) *Idem:* Ibid. **30:** 881, 1933. (6) *Idem:* Endocrinology **17:** 550, 1933. (7) *Idem:* Am. J. Physiol. **106:** 238, 1933. (8) *Wallen-Lawrence, Z., and Van Dyke, H. B.:* J. Pharmacol. & Exper. Therap. **43:** 93, 1931. (9) *Zondek, B.:* Klin. Wchnschr. **9:** 1207, 1930. (10) *Fluhmann, C. F.:* Am. J. Physiol. **108:** 498, 1934. (11) *Smith, P. E.:* Am. J. Anat. **45:** 205, 1930. (12) *Pencharz, R. I., and Long, J. A.:* Am. J. Anat. **53:** 117, 1933. (13) *Engle, E. T.:* J. A. M. A. **93:** 276, 1929. (14) *Orban, F., and Watrin, M.:* Compt. rend. Soc. de biol. **100:** 438, 1929. (15) *Hamburger, C.:* Studies on Gonadotropic Hormones, Copenhagen, 1933, Levin & Munksgaard. (16) *Selye, H.; Collip, J. B.; and Thomson, D. L.:* Endocrinology **17:** 494, 1933. (17) *Collip, J. B.; Selye, H.; Anderson, E. M.; and Thomson, D. L.:* J. A. M. A. **101:** 1553, 1933. (18) *Noguchi, Ko.:* Jap. J. M. Sc. Pharmacol. **5:** 104, 1931. Quoted by Collip et al.[19] (19) *Collip, J. B.; Selye, H.; and Thomson, D. L.:* Nature **131:** 56, 1933. (20) *Smith, P. E., and Leonard, S. L.:* Proc. Soc. Exper. Biol. & Med. **30:** 1248, 1933. (21) *Fluhmann, C. F.:* J. A. M. A. **93:** 672, 1929. (22) *Idem:* Am. J. Obst. & Gynec. **20:** 1, 1930. (23) *Idem:* Endocrinology **15:** 177, 1931. (24) *Zondek, B.:* Klin. Wchnschr. **9:** 393, 1930. (25) *Idem:* Klin. Wchnschr. **9:** 679, 1930. (26) *Frank, R. T.:* Am. J. Obst. & Gynec. **24:** 932, 1932. (27) *Leonard, S. L., and Smith, P. E.:* Proc. Soc. Exper. Biol. & Med. **31:** 283, 1933. (28) *Rössler, H.:* Ztschr. f. Geburtsh. u. Gynäk. **96:** 516, 1929. (29) *Zondek, B.:* Klin. Wchnschr. **11:** 274, 1932. (30) *Ferguson, R. S.:* Am. J. Cancer **18:** 269, 1933. (31) *Evans, H. M.; Simpson, M. E.; Austin, P. R.; and Ferguson, R. S.:* Proc. Soc. Exper. Biol. & Med. **31:** 21, 1933. (32) *Corner, G. W.:* Medicine **12:** 61, 1933. (33) *Fluhmann, C. F.:* Northwest Med. **33:** 10, 1934.

2725 Filbert Street

Haselhorst: The Genesis of Endometriosis with Special Consideration of the Endometriosis Recto-cervicalis, Ztschr. f. Geburtsh. u. Gynäk. **105:** 1, 1933.

From clinical observations and experimental studies it must be deducted that both endometrial and tubal mucosa are invested with marked tendencies of invasion and implantation. Outside of the possibility of mucosa being expelled from the tubal ostium during menstruation and in the interval, there are many other opportunities for implantation into the abdominal cavity. Such are given at the time of tubal and uterine resections, myomectomies, perforations, cesarean sections and even simple curettements.

Compared with vagina and abdominal wall the peritoneum is more resistant toward implantation, probably has defensive powers against foreign cells.

The culdesac is predisposed for implantation and invasion, because the sero-epithelium has lost its resisting power through frequent accumulation of blood, follicular fluid and cell detritus, which all act as irritants to the epithelium.

Serial sections of three cases in which the entire culdesac was extirpated show that the endometriosis of the rectovaginal septum was always due to an invasive growth from the culdesac. The endometrial tissue could be followed continuously from the surface of the culdesac down to the lesion in the septum.

Grover Liese.

THE INFLUENCE OF PREGNANCY ON TUMOR GROWTH*

L. A. Emge, M.D., San Francisco, Calif.

(From the Department of Obstetrics and Gynecology, Stanford University School of Medicine)

CLINICAL and experimental investigators have earnestly striven for years to solve the vexing problem dealing with the influence of pregnancy on benign and malignant tumor growth. The firmly established opinion that pregnancy invariably hastens or stimulates tumor growth is receiving less and less support from those who have critically analyzed clinical or experimental studies. The accumulated literature is very extensive. It is presented here under various subject headings, with a separate grouping of clinical and experimental reports. We are adding to them clinical findings collected from the records of the Department of Obstetrics and Gynecology of the Stanford University School of Medicine, as well as our observations on experimental tumor growth in pregnancy.

CLINICAL STUDIES

Cancer of the Uterus.—Cancer of the uterus associated with pregnancy is an infrequent occurrence and usually originates in the cervix.

Gross collected statistics embodying 120 cervical carcinomas in 224,080 pregnancies, or 0.053 per cent. He reports the incidence of cervical carcinoma in pregnancy at the Kiel University Clinic as 0.065 per cent. Further figures appearing in the literature are as follows:

Stockl (Posen) 0.044 per cent; Biro 0.047 per cent.

Biro's collected statistics: Maltmüller (Basel), 0.02 per cent; Schweitzer (Leipzig), 0.05 per cent; Küstner (Breslau), 0.09 per cent; Büben (Budapest), 0.026 per cent; Hauch (Copenhagen), 0.016 per cent; Schaaning (Oslo), 0.011 per cent; Katz (Vienna), 0.03 per cent; DeLee (Chicago), 0.007 per cent.

Hinselmann's collected statistics: Lindquist, 1 in 2,000 (0.05 per cent); Zimmermann, 1 in 1,200 (0.083 per cent); Low Maternity Brooklyn Hospital, 1 in 1,500 (0.067 per cent); Von Winckel, 7 in 18,000 (0.039 per cent); Stratz, 7 in 5,000 (0.14 per cent); Müller, 6 in 3,000 (0.2 per cent); Tiltsch, 10 in 26,584 (0.037 per cent); Franz, 14 in 700 (2 per cent); C. Schröder, 12 in 1,034 (1.16 per cent).

Hinselmann estimated that only 1 per cent of all cancers of the uterus occur during pregnancy. Similar figures arrived at by others are cited by him: Katz, 1.18 per cent; Williams, 1.57 per cent; Glockner, 1.79 per cent.

The incidence of cancer of the cervix occurring with pregnancy observed in the clinic and private services of the Department of Obstetrics and Gynecology at the Stanford University School of Medicine is 0.05 per cent, or 6 in 11,600.

---

*Supported in part by a grant from the Rockefeller Fluid Research Fund of Stanford University School of Medicine and from the Committee on Scientific Research of the American Medical Association.

NOTE: For lack of space it was necessary to omit the valuable and extended bibliography, which may be found, however, in the current volume of the Society's Transactions and the author's reprints.

Peller compared the expected number of neoplastic growths in pregnant women, estimated on the basis of known figures for carcinoma in various age groups of nonpregnant women, with the actual occurrence of carcinoma in pregnancy and found that the actual occurrence was significantly lower than expected. His study constitutes an interesting analysis of the figures of British mortality statistics on cancer. In his final conclusions Peller expressed the belief that pregnancy leaves the general body structure more resistant to the development of cancer, raises the average age of cancer occurrence, and retards its progress. It is his opinion that this is the expression of a protective mechanism either produced or intensified by gestation. These conclusions essentially substantiate the contentions of A. Mayer, which are based on a study of 56 patients. Mayer's critical analysis was largely instrumental in upsetting the long-established idea that pregnancy inevitably hastens the growth of uterine cancer. In his final conclusions, Mayer expresses the belief that pregnancy certainly does not favor the growth of cervical carcinoma but that in fact it restrains its spread and increases its operability and curability. In explanation, he cites Senator and Kaminer's theory of the existence of a protective mechanism against cancer possessed by youth which, when ineffective, expresses itself in an increased virulence of growth. He also makes reference to Ehrlich's theory of athrepsia.

Ehrlich contended that the avidity of the neoplastic cell was inhibited by the greater avidity for food of the growing cell mass of the fetus. If the cancer mass, nevertheless, manifests virulent growth, it may be presumed that the inherent protective mechanism is inefficient and that the avidity of the cancer cell is greater than that of the fetus. Mayer does not deny the possibility that there may occur a disturbance in hormonal balance during pregnancy which can influence neoplastic growth, as contended earlier by Fichera, and others.

Mayer's conclusions, which are quite in contrast to the firmly rooted impression that pregnancy has at all times an unfavorable influence on cancer (Bainbridge), are by no means shared by all subsequent investigators (Lederer, Gross, Vignes, Schweitzer, Audebert and Galy-Gasparrou, von Franqué, DeLee, Crossen, Clark and Norris, Bell, Peller, Roy, Emery, Lynch and Maxwell). Others have substantiated his views, wholly or in part, and have presented evidence to prove that pregnancy does not necessarily increase the degree of malignancy or favor the spread of cancer, but that depending on the type of cancer, the age of the host, and the period of discovery, pregnancy in fact may be considered a favorable factor (Edelberg and Galant, Sommers, Weibel, Fellner, Wolff, Stiglbauer, Peller, and Mundell). There are others, however, who are convinced that pregnancy does not influence cervical cancer one way or the other (Stockl, Biro).

O. Frankl, Schilling, Weibel, Sommers, Schumann, Katz, Pouey, Condamin and Voron and Molin, McGlinn, Piper, von Franqué, Hinselmann, Biro, Nevinny, Vignes, Ducuing and Guilhem, while withholding final conclusions, concede that pregnancy does not necessarily hasten the growth of cervical cancer but may favor its spread because of the more favorable conditions created by the increased blood and lymph supply. It is admitted, also, that in pregnancy mature types of cancer in older individuals, when discovered early, offer a better prognosis for ultimate recovery than in the nonpregnant state.

It is difficult to say how important the age factor is in respect to cancer resistance. Cancer in the young is frequently very vicious, and therefore youth is an added factor against ultimate recovery (Clark and Norris). By far the greater number of cases reported fall in the thirty- and forty-year age group (Gross, Wolff, Peller). It therefore is reasonable to assume that cancer in young pregnant women assumes a particularly rapid course, not necessarily because of the pregnant

state but because of existing growth conditions inherent in cancer of the young. Ducuing and Guilhem, without venturing an explanation, state that cancer of the cervix during pregnancy is more frequent among multiparas than primiparas.

If pregnancy is an exciting factor in uncontrolled tissue growth, i.e., malignancy, it would be reasonable to expect cancer to occur in ectopic gestation more frequently than it does. The infrequency of this occurrence is apparent from the small number of cases reported in the literature (Goldberger, Batisweiler, Rech, Pokrovsky, Riedinger, Hirschberg, Maršalek, Tracy, and H. H. Schmid).

Taking all factors into consideration, the probability suggests itself that pregnancy does not necessarily exert an unfavorable influence on the course of cervical cancer, but that the great virulence of cancer in young pregnant women depends upon some other biologic factor. While the local increase in blood and lymph supply incident to pregnancy offers a more fertile soil for invasion by neoplastic growth, it also favors operability, and therefore curability.

There is no proof, so far, that in the human a growth hormone such as that described by Evans and Smith bears a direct influence on cervical cancer (Wagner).

Because our actual experience with cancer of the cervix in pregnancy is limited to only six cases, we present our findings and deductions merely as a matter of record (Table I). Cases 1 and 6 came under observation because of uterine bleeding. Pregnancy was discovered during treatment. Case 5 went to term without symptoms, although an angry erosion was noticed in the seventh month of pregnancy. It was treated until the ninth month, when treatment was discontinued because of approaching term. Four weeks after delivery the patient returned because of bleeding, and the cervix was cauterized. Ten days later a biopsy proved the condition malignant. In Case 4 uterine bleeding began after the third month of pregnancy. In Case 2 bleeding appeared in the seventh month, and the patient was delivered by cesarean section. In Case 3 the patient noticed irregular bleeding soon after the first missed period.

In Cases 1, 3, 4, and 6 it is quite reasonable to suppose that cancer was present prior to gestation. It is not possible to say this of Cases 2 and 5, and if it was present, it certainly must have been held in check. The patient in Case 5 returned four years later with an adenocarcinoma of the Bartholin gland, which was removed radically and so far has not recurred.

The outstanding feature of this small series is the high incidence of cure, five out of six patients being alive five years or more. The age of the patient and the type of cancer in Case 1 speak for primary virulence of growth and not necessarily for an exciting factor introduced by pregnancy.

This series is entirely too small to make any definite statements relative to the influence of pregnancy on the growth of cervical car-

TABLE I. STANFORD SERIES OF CERVICAL CARCINOMAS ASSOCIATED WITH PREGNANCY

CASE NO.	LAB. NO.	AGE	GRAV.	PARA	MONTH OF PREGNANCY	TYPE OF CANCER	DEGREE OF MALIGNANCY	CLINICAL CLASSIFICATION	TREATMENT	RESULT
1	5177	25	iii	ii	2	Squamous	Immature	Inoperable	Radium	Died at end of 4th yr.
2	A-3918	32	vi	v	7	Squamous	Immature	Borderline	Radium and x-ray	Alive 5 yr. later
3	3293	38	v	iv	4	Adenocarcinoma	Mature	Operable	Hysterectomy	Alive 6 yr. later
4	A-3496	36	iii	ii	4	Adenocarcinoma	Mature	Borderline	Hysterectomy	Alive 6 yr. later
5	A-3565	37	i	i	Term	Squamous	Midmature	Operable	Radium	Alive 7 yr. later
6	A-4962	38	i	0	3	Squamous	Immature	Operable	Radium	Alive 5 yr. later

cinoma. Certain factors discussed, however, are quite in harmony with the conclusions of A. Mayer.

Sarcoma of the Uterus.—Sarcoma of the uterus during pregnancy is very rare. Hesseltine, Hardouin and Brault, and Patel and Eparvier are all of the opinion that the growth of this neoplasm is accelerated during gestation. Hesseltine ascribes this to the increased vascularity of the uterus.

Chorioepithelioma.—Jacob reports one case. He states that chorioepitheliomatous remnants or metastases may exist in a latent state, to be activated by a subsequent pregnancy. In this instance it is quite possible that growth occurred because of a functional or hormonal stimulus incident to pregnancy.

Cancer of the Vagina.—Tuft reports such a case in a girl sixteen years old, seen late in pregnancy, and Audebert and Estienny report a case of a multipara, thirty-three years old, at term. Tuft assumed that the tumor originated in epithelial rests of the Wolffian ducts, which, under the stimulus of pregnancy, assumed proliferative tendencies. The marked increase in vascularity must be considered another important factor, although its manifestations may be only of a temporary character. Proof for this has been offered by Kamniker in the study of elephantiasis, which is aggravated by pregnancy but regresses immediately after its termination.

Cancer of the Urethra and Bladder.—This condition is very rare in pregnancy. Eichenberg and C. Müller report one case each of cancer of the urethra. Carcinoma of the bladder is described by Waser. In each instance pregnancy was thought to have exerted an unfavorable influence. Müller, although attributing the very rapid growth to an activating factor introduced by gestation, admits that this particular type of cancer might have been a fast growing neoplasm in the beginning. As in the case of vaginal neoplasms, the possibility that pregnancy favors cellular activity because of an increased blood and lymph supply should be given serious consideration.

Benign and Malignant Tumors of the Breasts.—It is well known that benign adenomas of the breast respond to the stimulus of pregnancy in the same ratio as does the normal mammary tissue. Such adenomas or fibroadenomas may become more evident during lactation because of accumulated secretion. They usually recede after weaning, although recession usually is slower than that of the normal tissue. This process repeats itself with each succeeding pregnancy (Hirst, Fitzwilliams, Kreibig, Ingleby, Kilgore and Bloodgood). Husted reports that such tumors may recur as fibromas and fibrosarcomas.

The activating factor necessarily must be of hormonal origin, and it is not surprising, therefore, that carcinoma of the breast is unfavorably influenced by pregnancy (Patel, Davis, Hirst, Barthelemy, Kilgore and Bloodgood, G. Wolff, Odermatt, Döderlein, Fitzwilliams). According to Fitzwilliams, there is no evidence that pregnancy or lactation is responsible for the inception of mammary neoplasms.

We have observed only one patient in 11,600 pregnancies with a mammary carcinoma. This patient, forty-six years old, gravida viii, para viii, was operated upon radically and treated with massive doses of x-ray elsewhere, previous to our observations. Two months later she conceived, and within one month local recurrences were noticed. The patient came to us in the sixth month of her pregnancy. Carcinomatosis was general and progressed rapidly. She delivered prematurely

one month later, and died within twelve days. The immediate recurrence and its very rapid spread strongly suggest that gestation enhanced the virulence of this growth.

Ovarian Tumors.—The coexistence of ovarian tumors and pregnancy is given as varying between 0.03 and 2.8 per cent in Kermauner's collected statistics. This coincides in general with figures by others (See A. Mayer in Halban Seitz, Vol. 5, 0.15 per cent to 1.5 per cent; Schwarzkopf, 0.03 to 0.4 per cent). In our department, the incidence is 27 in 6,263 clinic deliveries, or 0.43 per cent. Figures from the private service, unfortunately, were not available. Cystomas constitute the major portion of this tumor group; the dermoids are next, to be followed in frequency by the malignant tumors which form a very small proportion; and last are the fibromas, which are very rare. Sarcoma of the ovary coexisting with pregnancy is practically unknown and usually is not diagnosed until the malignancy is far advanced (Goecke). With the exception of isolated occurrences, tumors of the ovary do not increase in size during pregnancy (Litzenberg, Spencer, Ingraham, Caverly, Davis, Giles, Piper, Forgue, DeLee). Occasionally an ovarian cyst may assume a very rapid growth, but the character of the epithelium is not changed. Most observers ascribe the enlargement to the remote influence of pregnancy, i.e., increased vascularity and mechanical distortion, and not necessarily to a functional response (Gilliam and Gilliam, Knebel, Sappey, Goldberger, Riche, Vayssiere, Acosta-Sison, McCullough, Bell, Forgue, Giles, Davis. See also Caverly's figures).

Dermoids ordinarily do not enlarge during pregnancy. The writer has observed two patients with bilateral dermoids, one of whom went through three pregnancies and the other through two without any change in size of the tumors. Cystic teratomas, on the other hand, may at times enlarge quite rapidly. Such a tumor was observed by us prior to and during pregnancy, and its sudden rapid enlargement in the sixth lunar month required removal. The blood supply to this tumor was very bountiful and there was a definite torsion of the pedicle with incarceration of the cyst. We explained this sudden enlargement on the basis of stasis, since cytologic studies did not reveal unusual secretory activity in the adenomatous elements of the cyst. No doubt certain ovarian tumors respond to a functional stimulus peculiar to pregnancy. One may conclude this from the occurrence of pigmentation in epidermal tissues so commonly present in dermoid tumors (Fischl). It is reasonable to assume, also, that since thecalutein cells undergo a marked hyperplasia during gestation (Kusuda), cysts originating from this component of the ovary can respond functionally to the stimulus of pregnancy. Probably there are other ovarian tumors, the cellular components of which may be susceptible to a hormonal stimulus of pregnancy, but there is no definite proof for such a contention.

There are recorded only a few cases of Krukenberg tumors observed during pregnancy. Turolt (quoting Burdsinski and H. H. Schmid), O. Frankl, and Puppel do not commit themselves as to the influence of pregnancy, but Esau and Goldberger are quite certain that pregnancy favors the spread of this neoplasm.

Fibroids of the Uterus.—The incidence of fibroids in pregnancy is still undetermined. It is most likely greater than recorded if the number of women seeking treatment for uterine fibroids, who have been pregnant one or more times, can be used as a criterion. Fervers cites Schauta, who reports 0.7 per cent in 100,000 deliveries, and R. N. Pierson, who estimated the occurrence as 0.8 per cent in 30,000 deliveries. We found that 81 out of 6,263 clinic patients delivered had fibroids (1.3 per cent). Figures from the private service were not available.

Many clinicians believe that certain fibroids enlarge or actually grow more rapidly during pregnancy. Others contend that pregnancy does not exert such an influence (Bell, Scipiades, Koster, Katz, Walther, Benner, and Young). Börner's studies have produced evidence that fibroids migrate toward the surface during the progressive enlargement of the uterus, and since their size is rarely determined before pregnancy, it is difficult to determine whether such tumors become more apparent because of a change in position, whether they enlarge temporarily in response to local changes, or whether they actually grow (Windeyer). Whatever the explanation, the fact remains that certain fibroids of the uterus enlarge rapidly during pregnancy. This, also, is true of fibromas of the mesentery (Antoine).

The mechanism involved in the enlargement of fibroids in pregnancy has been explained on several bases. Williams, DeLee, Heimo, Polak, Lockyer, Vaudescal, and Mosher attribute it to hypertrophy and edema. Spencer, Lynch, Frank, and Cragin add to this the factor of hyperplasia. The stimulus of pregnancy and an increased blood supply are favored by Reed, Ashton, Bland-Sutton and Giles, and Sheddan. Herman, Bandler, Graves, and Cragin consider the enlargement, particularly in pure myomas, as a purely functional response in which the tumor shares the growth of the parent tissue (uterus). In this connection, however, Ferguson points out that certain tumors enlarge beyond a reasonable fulfillment of the potentialities of pregnancy. In general, many observers accept the view that the enlargement of these tumors is a concomitant of pregnancy (Green, Stevens, Clark and Norris, Karsner, Edgar, Anspach, Thompson, Theron, Goldstein, Holmes, Litzenberg, Harris, and Cameron). That most of these neoplasms rapidly regress during the involutionary period of the uterus is an established fact. It is interesting that in subsequent pregnancies, not all of these tumors show the same tendency to enlarge which may be the result of vascular and cellular damage produced during the first involution. The complete disappearance of fibroids after pregnancy has been observed by Lynch, Watson, Pouey, Barnes, and Bublitschenko, although Bland considers this highly improbable. Whether the enlargement of fibromyomas during pregnancy is actually due to a functional response or results from an increased vascularity which invites hypertrophy, hyperplasia, and edema, remains, therefore, an open question. Involution of these tumors can be readily explained on either basis.

There is no evidence that pregnancy alters the character of the cellular components of these neoplasms, for sarcomatous degeneration as a result of pregnancy is unknown. McLean's radical stand that

these tumors should be removed immediately upon diagnosis because "the fibroid of today may be a sarcoma later" is not tenable.

A survey of our own material leads us to believe that only few of these tumors reach a considerable size during pregnancy. Although some of them were discovered early in pregnancy, we could not determine how much they had enlarged up to the time of discovery, nor could we estimate their primary growth-rate. We are unable, therefore, to say to what extent pregnancy actually influenced the enlargement of these tumors. However, we are under the impression that the tumors which actually increased in size while under our observation did so in a ratio equal to the enlargement of the uterus. We are convinced, also, that most fibroids, with the exception of some pedunculated tumors, regress very materially during the puerperium, some to a very insignificant size and others to a point where, some months after delivery, they no longer can be felt. Our observations leave us with the impression that in subsequent pregnancies fibroids often fail to enlarge, or that the degree of enlargement is considerably less than that of the first gestation.

As to the mechanism of enlargement, we have studied tumors removed at various periods of pregnancy. Venous stasis, edema, both intercellular and intracellular, and progressive hyaline degeneration become more evident with the advancement of pregnancy, but apparently do not progress materially after the seventh lunar month although degeneration beyond hyaline changes may continue. Hypertrophy is confined to muscle fibers and reaches its height somewhere between the fourth and sixth months. The apparent increased size in connective tissue elements seen in some tumors is due to intercellular edema. Vacuolization of cells is therefore commonly observed. That an actual hyperplasia is responsible for this increase could not be determined by us. We doubt, however, that the enlargement of fibromyomas during pregnancy, because of the subsequent and rapid regression, signifies a true growth phenomenon. We are inclined to believe that it is a temporary response, due partly to functional hypertrophy of muscle cells and partly to increased vascularity. We believe, also, that Börner's theory of tumor migration deserves serious consideration in this connection.

Cancer of the Gastrointestinal Tract.—Peller and Stöhr, in reviewing the report of Sir George Buchanan of the British Cancer Commission, state that the behavior of gastrointestinal cancer during pregnancy is far from uniform and that it is impossible, therefore, to come to a final conclusion. It is their impression, however, that this type of cancer at times grows more rapidly during gestation, which opinion is shared by Katz and Kaspar.

Gastrointestinal cancer during pregnancy is very rare. When it occurs in the young, it usually is very virulent. This, perhaps, is the

important factor, for Peller's review does not prove that cancer of the digestive tract acts differently in pregnancy from what it does in the nonpregnant state at various age levels. It is reasonable to assume that cancer of the gastrointestinal tract takes part in the general and local reactions concomitant to pregnancy.

Respiratory Tumors.—Tumors of the upper respiratory tract during pregnancy are extremely rare. Manasse reports one case of tumor of the pharynx, which apparently was not influenced by pregnancy.

Granulomas.—Paviot, Levrat, and Jarricot report observations on Hodgkin's disease, from which they conclude that repeated pregnancy hastens the development of the disease. Granuloma inguinale, on the other hand, is influenced by pregnancy only to the extent of the general body reaction (Bland).

Neurofibromatosis and Epulides.—Both of these neoplastic developments take part in the general tissue response to gestation. All writers agree that the lesions of neurofibromatosis (von Recklinghausen's disease) become more evident during gestation because of the noticeable increase in pigmentation, which disappears during the puerperium (Moreira, Burg, Kushner, Schultze, Fischl). Neurofibromatosis responds similarly to lipomatosis symmetrica, angiomas and lymphangiomas. This, according to Fischl, must be interpreted as a transitory reaction to pregnancy and not as a true growth phenomenon. Essentially the same holds good for epulides which appear with pregnancy, spontaneously disappear between two and three months after delivery, and recur in subsequent gestations (Blum).

Brain Tumors.—Very few cases of brain tumor during pregnancy are on record (Novak), and the uncertainty of their growth behavior is well known. The literature was reviewed by Bickenbach, who does not venture an opinion on the influence of pregnancy on brain tumors as a group. He points out, however, that symptoms at times appear with pregnancy and totally disappear after delivery, to recur in subsequent pregnancies, and that one might interpret this, not necessarily as a growth phenomenon, but as the ability of nerve tissue to take part in the general cellular response to pregnancy. Fleischmann shares this opinion.

Tumors of the pituitary gland, particularly those of the anterior portion, respond to the stimulus of pregnancy but at times go beyond the expected potentialities of cellular response (Vejdovsky, Winter, Morhardt). They act similarly to cancer of the breast, in which functional hyperplasia hastens the growth of an already unorganized and uncontrolled neoplasm.

EXPERIMENTAL STUDIES

There are available a number of reports from experimental laboratories which deal with biologic principles underlying growth behavior

of transplantable and spontaneous tumors during pregnancy. They are summarized here in chronologic order (Table II). The conclusions recorded strongly support clinical evidence, and in general attribute to pregnancy either a retarding or an impassive rôle.

The variety of tumors used in these studies shows that different tumors may exhibit different degrees of susceptibility to the influence of pregnancy. The results, therefore, seem to be contradictory, but in fact only express differences in individual tumor behavior. This is well demonstrated by the results reported by Loeb of his experiments with transplantable adenofibroma in the white rat and in the dog.

TABLE II

YEAR	OBSERVER	TYPE OF TUMOR	ANIMAL	EFFECT OF PREGNANCY ON GROWTH		
				STIM.	INHIB.	NONE
1894	Morau	Carcinoma	Mouse	+		
1902	Loeb	Mammary adenoma	Rat	+		
1902	Loeb	Sarcoma	Rat	+		
1902	Loeb	Mammary adenoma	Dog		+	
1902	Herzog	Loeb sarcoma	Rat	+		
1904	Bashford and Murray	Jensen sarcoma	Rat			+
1907	Haaland	Various sarcomas	Mouse		+	
1908	Ehrlich	Carcinoma	Mouse		+	
1909	Uhlenhuth and Weidanz	Carcinoma	Mouse		+	
1909	Albrecht and Hecht	Carcinoma	Mouse			+
1914	Von Graff	Carcinoma	Mouse			+
1916	Loeb and Fleisher	Mammary carcinoma	Mouse		+	
1920	Slye	Spont. carcinoma	Mouse		+	
1921	O. Frankl	Carcinoma	Mouse		+	
1921	Kross	Flexner carcinoma	Rat		⊕	+
1924	Kok	Ehrlich carcinoma	Mouse		+	
1924	Krotkina	Tar papilloma	Rabbit	+		
1925	Kamekura	Carcinoma	Mouse		+	
1929	Marsh	Spont. carcinoma	Mouse		+	
1931	Mischtschenko	Sarcoma	Rat		+	
1931	Mischtschenko	Carcinoma	Rat		+	
1932	Grauer and Robinson	Fibroadenoma	Rat	+		
1933	Emge and Wulff	Fibroadenoma	Rat			+
1933	Emge and Wulff	Fibroma	Rat			+
1934	Emge and Wulff	Fibrosarcoma	Rat			+

For a number of years we have been studying growth behavior of transplantable tumors in the white rat. Part of this study deals with the influence of pregnancy (Emge and Wulff).

Our observations in this study were confined to the growth behavior during pregnancy of adenofibromas, fibromas, and fibrosarcomas originally derived from a spontaneous adenofibroma of female white rats. Details of transplantation and development were published in a previous article (Emge and Wulff). The tumors developed by us appear as single tumors and, because of their steady and uniform growth, are especially suitable for observation. The fibrosarcomas do not metas-

tasize but recur rapidly after removal. This is typical of many transplantable sarcomas of the white rat. We previously reported that the adenofibroma and fibroma strains responded functionally to the stimulus of pregnancy, as evidenced by secretory reactions and by the appearance of reticuloendothelial cells and macrophages, respectively. The response of the sarcoma did not go beyond that of the body response in general, as manifested by edema and an increased vascularity, which was observed also in the benign tumors.

Until we made volumetric studies, we, too, were under the impression that transplantable adenofibromas and fibromas grew more rapidly during pregnancy and lactation since we observed in our cytologic

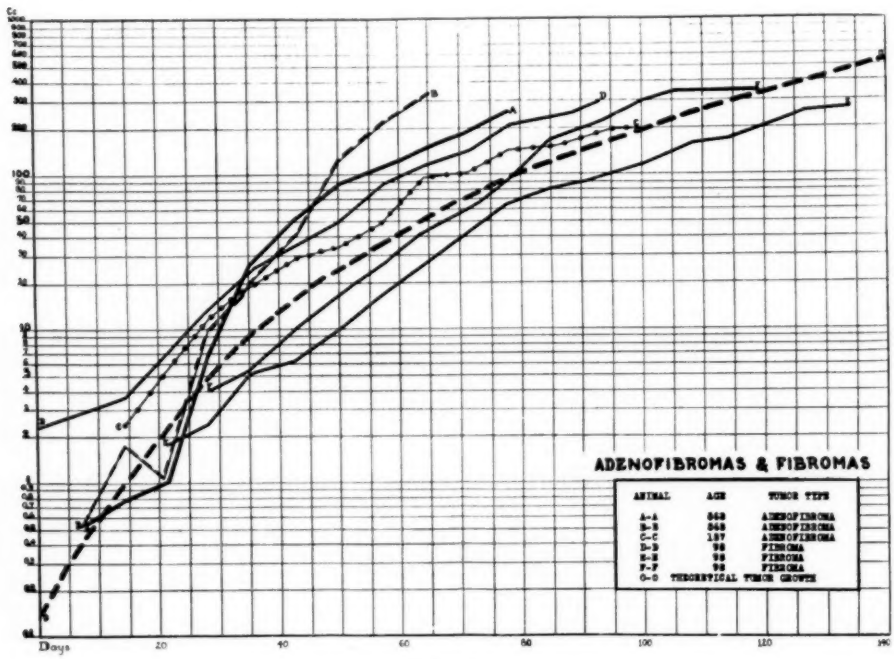


Chart 1.

studies that the adenomatous element of these tumors responded to pregnancy in exactly the same way as normal mammary tissue. Only after making volumetric calculations did we discover the fallacy of this assumption.

Our first studies, based on weekly measurements, were repeated on the basis of daily determinations. Tumor volume was determined according to the prolate spheroid formula $4/3\ \pi\ ab^2$. Growth curves were recorded on 4-cycle semilogarithmic paper and are presented in the accompanying charts.

Charts 1, 2, and 6 represent typical growth-rate curves of benign and malignant tumors in nonpregnant animals, while Charts 3, 4, 5, and 7 represent typical curves of the growth rate of different tumor

groups as influenced by pregnancy. While individual variations in the growth rate of slow growing fibromas and adenofibromas occurred during gestation, they differ little from those which occurred in the

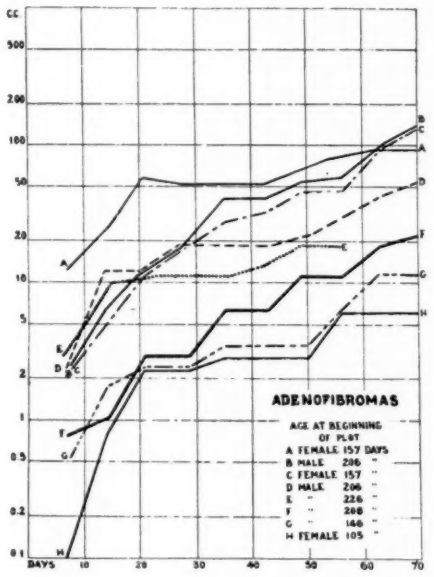


Chart 2.

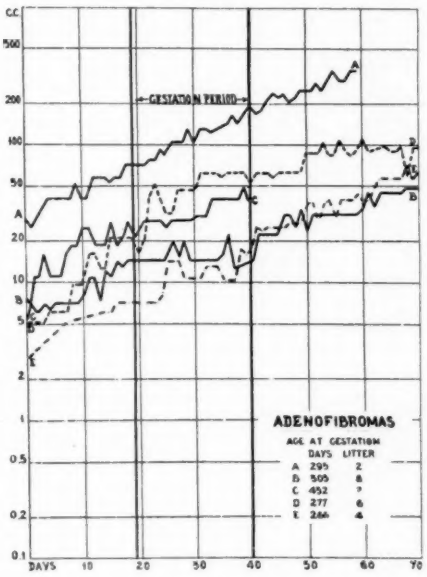


Chart 3.

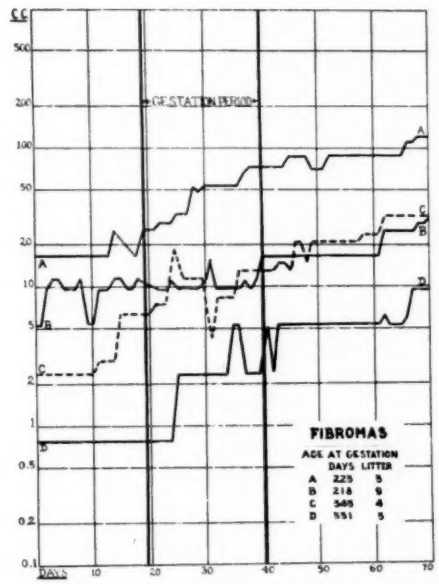


Chart 4.

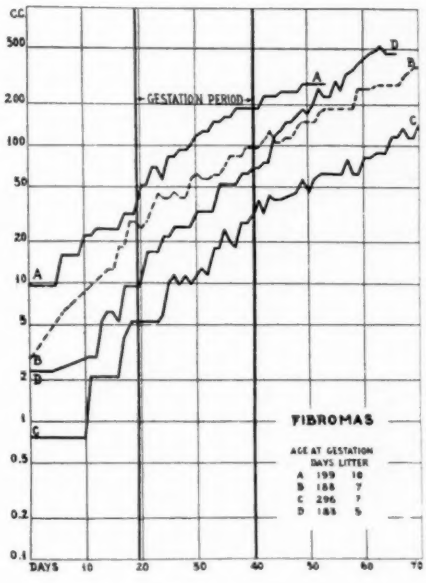


Chart 5.

nonpregnant state. Essentially, the inherent growth rate was maintained, although very small fibromas at times showed an unusual speeding up during the gestational period. In comparing slow to fast

growing fibromas, it is interesting to note that the faster growing tumors showed a more uniform growth behavior (Chart 5).

The size of the litter is recorded on each chart. The minor variations in the growth curves cannot be readily explained on the basis of differences in the size of the litters.

We recently completed a study dealing with the influence of pregnancy on the growth of the fibrosarcoma previously referred to. The same rapid and uniform growth rate was observed in the primary as in the recurrent tumors (Chart 6). We found it difficult to breed many animals because of the rapid enlargement of the tumors, which acted as a mechanical obstacle to copulation. Where we succeeded, we found that the growth rate was not influenced by gestation (Chart 7).

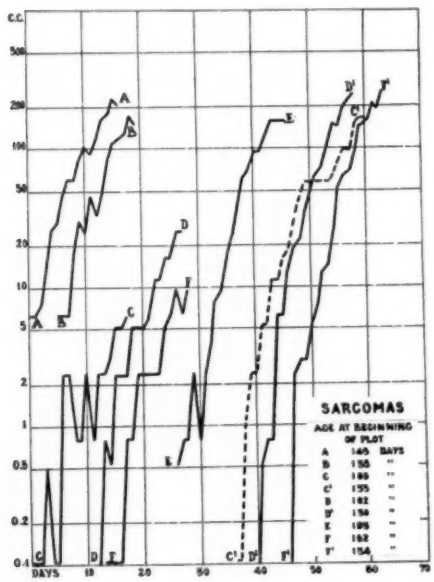


Fig. 6.

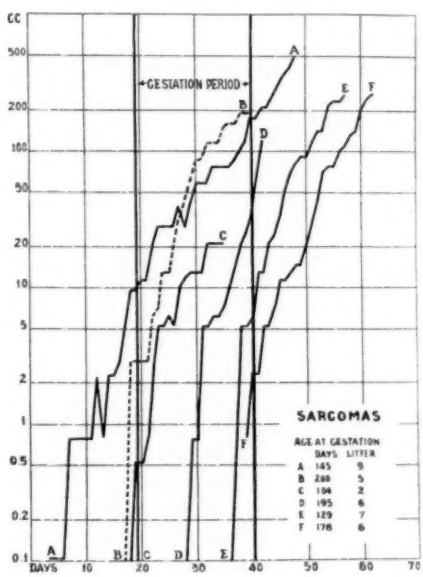


Fig. 7.

Comparison of our two series resulted in essentially the same findings, namely, that the growth rate of these neoplasms was not accelerated by pregnancy but is inherent in a given type. Minor differences occurred, but they are not of much significance because similar differences occurred in the nonpregnant state.

In a previous study of young ninety-day animals, we observed that during gestation the growth of benign tumors was slightly retarded but resumed its normal rate with the termination of pregnancy. We did not find this in the older animals with larger tumors. This strongly suggests that pregnancy enhances the action of a protective mechanism in the young.

We are unable to say that the size of the gestational mass influences the growth of the neoplasms we studied.

We conclude from our experimental studies to date that the growth rate of benign and malignant tumors, although responsive to the general systemic influence of pregnancy as expressed by cytologic changes, is not influenced beyond variations in individual growth propensities. Our findings, in general, are in harmony with those of Bashford and Murray, Albrecht and Hecht, Kross, and von Graff.

DISCUSSION

The evidence presented warrants the conclusion that the behavior of neoplastic tissue during pregnancy is dependent upon a complex set of factors. Experimental evidence strongly supports the belief that neoplastic tissue possesses definite and inherent growth propensities which are controlled by a protective mechanism peculiar to body economy. Regardless of the type of tumor the growth rate, therefore, depends upon a certain balance between these two factors. If this balance is disturbed, it will manifest itself in either an acceleration or retardation in the growth propensities of the neoplastic tissue. A knowledge of the primary growth propensities of a given neoplasm is therefore necessary for a correct interpretation of its growth rate during pregnancy. Since this is always difficult and, in fact, frequently impossible to gain in clinical studies, individual interpretations rather than definite biologic facts have been offered as criteria in the interpretation of growth phenomena of neoplasms in the human during pregnancy. It is, therefore, not surprising that the variance in opinions has materially retarded the clarification of the issue. Although there is, seemingly, contradiction in experimental evidence, the facts presented are necessarily more reliable and less subject to individual interpretation. It is quite true that evidence on the one hand deals with man and on the other with lower mammals and that the durations of pregnancy and the types of tumors observed differ materially. Granted that these factors are important, it nevertheless remains true that the basic biologic behavior of either the normal or neoplastic cell mass is constant. We, therefore, have to fall back on experimental evidence in order to clarify clinical deductions.

After all factors are taken into consideration, there remains no doubt that neoplastic tissue shares in the general systemic response to gestation. The ability of a given tumor to respond to variations in metabolism, tissue fluid, and blood volume therefore determines the extent of response. These changes may be microscopic in character, or they may assume macroscopic proportion.

If a tumor participates extensively in the local increase in blood and lymph supply, it increases proportionately in size as pregnancy progresses. This phenomenon is most often seen in connection with fibromyomas and certain ovarian cysts. It is not a true growth phenome-

non but a temporary response, the extent of which is dependent upon the ability of the neoplasm to take part in local changes.

Certain neoplastic tissues undergo hyperplasia and hypertrophy because of their ability to respond to changes in hormonal balance. This occurs most frequently in adenomatous tumors of the breast and in pure leiomyomas and adenomyomas of the uterus. It represents a true but temporary and limited growth response and may materially increase the growth rate of malignant tumors beyond the expected growth propensities. Because of the relatively long gestational period in man, the ultimate result is proportionately more evident than in the lower mammals. This fact should be taken into consideration when comparing clinical and experimental observations. As far as is known at this time, tumor growth is not accelerated by a specific growth hormone produced during pregnancy.

Retardation of tumor growth consequent to pregnancy has been observed by both clinical and experimental investigators, and has been explained on various grounds. Several investigators attribute an inhibitory faculty to the placenta and embryonal tissue (Fellner, Gross and Wajda, Fichera et al.) and to the marked increase in prolan during gestation (Zondek, and Zondek and Hartoch). Ehrlich, Slye, and others claim that the ability of the rapidly growing gestational mass to divert food from the neoplasm to itself (athrepsia) is an important inhibitory factor. It certainly cannot be the only factor because it can be nullified by the size and the growth rate of the neoplastic mass, as shown by Kross and also our own experiments. The theory of athrepsia is readily applicable where the size of the tumor and its growth rate are less than that of the fetal mass. Although both Ehrlich and Slye claim that this phenomenon inhibits or even prevents the growth of mouse cancer, it has been shown by numerous other investigators that in general it is a temporary phenomenon. The retardation of growth is to be interpreted on the basis of local starvation, for it can be overcome by the feeding of large amounts of vitamins (E. Fränkel and Gereb).

It has been frequently suggested that youth may possess a protective mechanism against tumor growth. The fact that the number of women afflicted with cancer during pregnancy is significantly lower than the expected number estimated on the basis of cancer mortality seems to indicate that pregnancy favorably influences such a protective mechanism. The complete lack of knowledge of the biologic factors of this protective mechanism against tumor growth leaves us with this most important problem still unsolved. There remains the fact that cancer during pregnancy, and particularly cancer of the cervix, does not only fall short of the expected number but also is particularly rare under the age of thirty, while between thirty and forty years its

curability is increased above the expected average. Also, this suggests the probability that pregnancy favors the retardation of cancer of the cervix, although it must be taken into consideration that age, time, location, and tissue type are factors which may play an important rôle in the behavior of this particular neoplasm. It would be faulty to base final deductions in regard to the influence of pregnancy on tumor growth solely on the behavior of cervical cancer in gestation. Nevertheless, the study of cervical cancer during pregnancy, because of its frequency and easy detection, has furnished us with more reliable data than cancer of any other region.

It is the writer's belief that regardless of the type of neoplasm, primary growth propensities are inherent, but vary in intensity. This applies to both controlled and uncontrolled neoplastic tissue growth.

There is no proof, whatsoever, that pregnancy alters the character of a given neoplastic cell beyond temporary reactions. Neither is there proof that pregnancy in itself is responsible for the inception of malignancy or for the malignant degeneration of benign tumors.

Therefore, when clinical deductions are compared with experimental observations we arrive at the following conclusions:

1. The influence of pregnancy on the behavior of neoplastic tissue depends upon a complex set of factors.

2. The growth rate of neoplasms is inherent, but the controlling mechanism is still unknown. Clinical evidence suggests that pregnancy favors a protective mechanism against tumor growth.

3. Neoplastic tissue takes part in the local and remote reactions incident to pregnancy, the ultimate result depending on the length of the gestational period. These changes are of a temporary nature. The extent of involution of benign neoplasms depends upon their relation to the generative organs, particularly the uterus.

4. Neoplastic tissue sensitive to hormonal stimuli may exhibit increased activity during pregnancy.

5. Physical changes in benign tumors during gestation are not necessarily expressions of growth activity.

6. It is not proved that pregnancy favors the inception of malignancy or the malignant degeneration of benign tumors.

7. Experimental evidence substantiates clinical findings in general, and permits the conclusion that pregnancy as a rule does not influence the growth rate or the size of neoplasms beyond certain reactions, of which retardation is the most frequent. In many instances it remains unaffected, and only occasionally an acceleration is observed. At the termination of gestation neoplasms assume their primary growth rate.

THE STATUS OF THE RESIDUAL TUBE FOLLOWING ECTOPIC PREGNANCY IN RELATION TO STERILITY AND FURTHER PREGNANCY

Analysis of 90 Cases Examined by Uterotubal Insufflation

I. C. Rubin, M.D., F.A.C.S., New York, N. Y.

IN OPERATIONS for tubal pregnancy, especially when rupture has taken place, the nonpregnant tube often escapes attention. The pregnant tube is identified and removed as rapidly as possible, the other tube receiving, as a rule, scant scrutiny.

Schumann[1] summed up the trend of American opinion on extrauterine pregnancy in his excellent monograph published in 1921. His own views with regard to treatment of the remaining tube coincided with the best gynecologic opinion of the time.

These views still hold for the treatment of ectopic pregnancy in multiparous women. In women whose only pregnancy is extrauterine and those who, besides having an ectopic pregnancy have borne a solitary child, the treatment requires modification. It is with this particular group that the present paper is concerned.

A more intensive interest in this group of sterile women has been brought about during the past decade by the following circumstances: 1. Haste at the operation for ectopic pregnancy has become less important since the difficulties of early diagnosis have been reduced. With the advent of newer tests for pregnancy, a definite decline in the occurrence of the tragic variety of tubal rupture is gradually taking place. 2. Exsanguination and shock are more easily combated by other measures besides blood transfusion which has since become almost routine. 3. Patients who have had an ectopic pregnancy have become more interested in their possibilities for future pregnancy and are demanding more and more to know what their chances are for repetition of the tubal pregnancy. The writer has met with several patients who are still seeking relief from secondary sterility though they were exposed to the hazards of repeated ectopic pregnancy. A larger number who are similarly interested have had the ectopic as their only pregnancy. 4. Plastic operations upon the fallopian tubes have been undertaken in the past few years to a greater extent than formerly. Success has followed tubal reconstruction in a small number of cases but in sufficient numbers to encourage in selected cases conservation and rehabilitation of the second tube. The most recent report in this connection is that

by C. C. Norris[2] who obtained 4 successful results following surgical treatment of occluded tubes.

Some idea as to the prospects of another tubal pregnancy or normal intrauterine pregnancy occurring in the same patient has already been obtained from statistical analysis of the past. Grouping the statistics from various authors Schumann[1] concluded "that among 280 patients in whom pregnancy of any kind was possible following tubal pregnancy, 35, or 12.5 per cent, had repeated ectopic gestation, while 134, or 47.8 per cent, had intrauterine pregnancies"; a ratio of about 1 to 4. R. R. Smith[3] analyzed cases of 1,608 patients operated upon by members of the American Gynecological Society and found the ectopic pregnancy repeated in 3.5 per cent. In his own series 14.6 per cent had a repeated ectopic pregnancy, and the number bearing living children was 32.6 per cent. Smith still feels that the second tube should be removed when children are not desired. Urdan[4] reported 27 repeated tubal pregnancies out of 474 cases from the gynecologic service at Mount Sinai Hospital. Brettauer and Peterson[5] have both reported 3 ectopic pregnancies in the same patient.

Of the 90 cases included in the present report, 23, or 25.5 per cent, gave a history of being pregnant again after a previous ectopic gestation. Fourteen of these later pregnancies were intrauterine, and 8 were again tubal. One of my patients developed an ovarian pregnancy one year after a previous tubal pregnancy.

Women who have had a tubal gestation exhibit a slightly lower fertility than the average woman. This is borne out by practically all the published reports. The incidence of sterility antedating the tubal pregnancy as met in the literature is a little more than 20 per cent (Foskett,[6] Rongy,[7] Masson,[8] Urdan[4] and others). In my series of 333 patients who became pregnant after treatment for sterility, 12 developed a tubal pregnancy; 4 of these had had a previous tubal pregnancy.

The present study is based upon an analysis of 90 patients who were operated upon for tubal pregnancy. All of these patients were examined by uterotubal insufflation after the operation, and a number of them were thus examined before and after the ectopic pregnancy. Thirteen patients did not desire to become pregnant again but were seriously interested to know whether conception was again likely to occur. They are included only from the viewpoint of their tubal status.

Only 33 out of these 90 patients had been pregnant previous to the tubal gestation. Inasmuch as the majority came for the relief of sterility, they were also examined by the routine steps involved in the comprehensive investigation of the problem in the sterile married couple. But in this paper only those points are considered which have a direct bearing on the status of the remaining fallopian tube. The study was undertaken in an attempt to ascertain whether it was not possible to

prognosticate the future obstetric fate of the patient and also whether the insufflation has some therapeutic value in this particular group of secondarily sterile women.

Four of the 77 patients were between the ages of twenty and twenty-five years; 39, between the ages of twenty-five and thirty years; 30, between thirty and thirty-five years of age; and 4, between the ages of thirty-five and forty years.

The length of sterility preceding and following the tubal pregnancies is given in Table I.

TABLE I. DURATION OF STERILITY

DURATION	BEFORE TUBAL PREGNANCY	AFTER TUBAL PREGNANCY
1 to 3 yr.	35 cases	20 cases
3 to 5 yr.	24 cases	26 cases
5 to 10 yr.	10 cases	26 cases
10 to 15 yr.	4 cases	2 cases
Not noted	4 cases	3 cases

Thus 38, or 52.05 per cent, had been sterile for three or more years previous to the tubal pregnancy, and 54, or 72.97 per cent, were sterile three or more years after the operation. It is noteworthy that 4 women had a tubal gestation after a primary sterility of more than ten years. Twenty-six women came for the relief of sterility from five to ten years after the operation for ectopic pregnancy and two women after a period of from ten to fifteen years.

Associated Abnormalities.—Pathologic changes which were present in the residual tube at the time of or before the tubal pregnancy and changes taking place after the operation may be held responsible for the fact that so many of these women remain sterile afterward. In this group the tubal lumen is more commonly obstructed without palpable disease than in the general group of sterile women. Palpable changes in the adnexa are recorded in 24 cases; uterine displacement, in 11; and cervical disease, in 11.

Menstrual abnormalities were frequently met. Of 87 patients whose menstrual type was noted, 25, or 28.73 per cent, had abnormal menses previous to operation and 35, or 40.23 per cent, following operation. Abnormalities (in all but 10 patients who complained of frequent and profuse periods) consisted of delayed and scanty menses. This high incidence of menstrual abnormality may be explained on the ground that the ovaries are often affected by the same pathologic processes that affect the tubes. The fact that the corresponding ovary was removed with the tube in 23 cases may explain the higher incidence of menstrual abnormalities following operation.

Types of Operation.—The 90 patients of this group were operated upon by 57 surgeons. Twenty-four were operated upon by the author.

Eight patients had bilateral tubal pregnancy. In 8 cases the side of the tubal pregnancy was not recorded; 44 were on the right side; and 30, on the left side. This agrees with the reported series of Lavell[9] and of Urdan.[4] Past attacks of appendicitis may be responsible for some of these right-sided tubal pregnancies, a view which is strengthened by the fact that in 21 cases, the surgeon deemed it necessary to remove the appendix in spite of the presence of blood in the peritoneal cavity.

Of other coincidental or previous operations which may have influenced the status of the residual tube the following are noted: hysteropexy in 5 cases and mobilization of the tube in one case. It must be borne in mind that the condition for which these operative procedures were performed, as well as the formation of postoperative adhesions, may possibly bear some etiologic relation to the production of tubal nonpatency.

Status of the Residual Tube as Determined by Insufflation.—Uterotubal insufflation was employed to determine the patency and function of the residual tube in 90 cases in which a history of ectopic pregnancy was obtained. The tubal status was studied: (1) in the main group; (2) the findings were compared with (a) those of the patients who had conceived after the ectopic pregnancy and (b) with those who did not again conceive and finally (c) the group of patients who became pregnant after insufflation.

When insufflation was performed soon after operation for tubal pregnancy, the residual tube was usually found to be in better condition than when a longer interval had elapsed; however, in a few cases the reverse was true. Sixteen patients were insufflated at various intervals after the operation up to two years. In 74 cases, or 82.22 per cent of the series, the tubes were insufflated two years or more following operation for an ectopic pregnancy, i.e., at a time when it may be assumed that the remaining tube had undergone as much change as the lesions could produce.

In one highly nervous woman the test was not completed. Eight patients with a history of bilateral salpingectomy were proved to have nonpatency. The insufflation was done at the urgent request of the patients. At the same time it was of interest to know whether a tube stump might still have remained pervious. The status of the 81 remaining cases is given in Table II.

Only 12.35 per cent of the tubes in this series showed normal patency, i.e., less than a third of the incidence of normal tubes generally encountered in sterile women. Inasmuch as some degree of patency of the only tube was present in 46 patients, the possibility of pregnancy was not excluded in 56.79 per cent. That tubal patency bears a definite relation to the potential pregnancy may be seen by comparing the find-

ings of the status of the residual tube in 23 patients who became pregnant after a primary ectopic gestation with the 67 nonpregnant patients.

TABLE II. TUBAL STATUS OF 90 CASES

	NUMBER OF CASES	PERCENTAGE
Normal patency	10	12.35
Nonpatency	35	43.21
Spasm and patency	3	3.70
Adhesions	22	27.16
Tubal stenosis	11	13.58
Total	81	100.00

TABLE III. COMPARATIVE STATUS OF POSTECTOPIC RESIDUAL TUBE IN RELATION TO SUBSEQUENT PREGNANCY

	PREGNANT AFTER AN ECTOPIC GESTATION	NOT PREGNANT AFTER AN ECTOPIC GESTATION
Normal patency	7	3
Spasm and patency		3
Stenosis		10
Closures	12	31
Incomplete		1
Adhesions	4	19
Total	23	67

Table III shows that the 23 patients who had another pregnancy after the first ectopic pregnancy had at least three times more normal tubes than the 67 patients who did not become pregnant again.

Seven of the 14 patients who had had an intrauterine pregnancy following the ectopic had normal tubes at a later examination. In 3 the tubes were adherent but patent and in four cases the tube was closed. The 8 patients who had repeated ectopic pregnancies showed bilateral closure. The patient who developed an ovarian pregnancy was insufflated both before and after the ectopic. At the first insufflation the tubes were found to be practically normal. The residual tube was later shown to be patent and adherent. The facts that the tubes were practically normal before the first tubal pregnancy developed and the later occurrence of an ovarian pregnancy on the side where the salpingectomy was performed suggest a possible ovular cause of the ectopic gestation. The case is too singular however for more than mere speculation.

The difference in the occurrence of repeated ectopic pregnancy as variously reported may be due, as Schumann[1] has pointed out, to different opportunities for the follow-up of these patients. The percentage in my own group is larger because it is taken from patients who came especially for the relief of sterility.

Normal intrauterine pregnancy may naturally be anticipated when the residual tube is found to be normally patent, but it by no means follows that another extrauterine pregnancy will necessarily occur when the tube is found to be impaired in patency and function. The findings with reference to this point are most interesting and suggestive.

Pregnancies Following Insufflation of the Residual Tube.—The 13 patients who were not interested in having children are omitted from this consideration. Twelve of the remaining 77 patients became gravid again after insufflation. Eight of these patients had had no other pregnancy than the tubal, 3 of the 12 patients had had term pregnancies and one, 2 miscarriages prior to the ectopic.

Four of the 12 had shown a residual adherent tube on insufflation; 5, a strictured tube; 2, a normally patent tube; and one showed spasm and normal patency. Of the 4 patients with an adherent residual tube, 3 developed intrauterine pregnancies and one, an ectopic pregnancy. Of the 5 with strictured tubes, one developed an intrauterine pregnancy; in one the outcome was not known, and 3 developed an ectopic pregnancy. The 2 patients with normal patency and the patient with spasm and normal patency had an intrauterine pregnancy.

In studying the pressure records it was found that in general where they were high, i.e., above 150 mm. Hg on one or more tests, though some degree of patency was present, the succeeding pregnancy was apt to be another ectopic. On the other hand when the pressures were lower, more approximating from 100 to 110 mm. Hg, the future pregnancy was more likely to be intrauterine. When the pressures ranged between 120 and 150 mm. Hg, the patient was likely to develop an extrauterine or intrauterine gravidity.* Twelve cases are obviously too small in number upon which to establish rules of prognosis. There are other factors to be noted in the insufflation, which will not be entered into at this time; they are awaiting further observation on a larger series. The following are the pressures in relation to the outcome of the pregnancy.

TABLE IV. OUTCOME OF PREGNANCY IN RELATION TO THE DEGREE OF TUBAL PREGNANCY IN 12 PATIENTS WITH A PREVIOUS ECTOPIC PREGNANCY

OUTCOME OF PREGNANCY		PRESSURES IN MM. HG
Intrauterine	8	62; 80; 90; 95; 100; 120; 145; 160
Ectopic	4	148; 190; 200; 200

Two patients became gravid at once after the test; 2, within two months; one, within three months; 3, within the second six months; one, two years later; and one, three years later. In addition, one patient became gravid at once following insufflation and again four and one-half years later following a second insufflation. Another became gravid five months after an insufflation and again two months following a subsequent insufflation. A therapeutic action may be ascribed to the insufflation in 5 cases.

*Of interest in this connection are 8 primary tubal pregnancies which followed treatment for sterility, including insufflation. In these 8 patients the tubes were found adherent or strictured at insufflation before the tubal pregnancy occurred.

The pregnancies terminated as follows: tubal pregnancy, 4; uterine pregnancy, 8. Six patients went to term; 5 were normal, and one ended in a stillbirth. In one case the outcome was not known. Nine of these patients had had no other pregnancy than the tubal. Two of the 12 patients had had an intrauterine pregnancy besides the ectopic gestation.

Localization of the Site of Obstruction.—It was usually possible to determine which tube had been removed and the exact site of the obstruction even when data on this fact were not available: (1) by insufflation with the aid of the kymograph; (2) by noting the location and radiation of the pain reaction during the insufflation; and (3) by abdominal auscultation.

When the solitary tube was normal, no pain was complained of or only the slightest midline pain or discomfort, comparable to mild menstrual cramps. When the tube was nonpatent or strictured, the pain reaction was referred to the tube remaining in situ and corresponding to the site of obstruction. By auscultation, it was often possible to hear the escape of gas from the fimbriated end. In general the sensory reactions were the same as those described when both tubes were present.

Pain reactions were carefully noted in 66 of 90 cases. In 4 cases in which both tubes were removed, midline pain was complained of. In 20 cases midline pain pointed to obstruction at the uterine end of the remaining tube. In 2 cases pain was referred to the side where a small piece of tube was left in situ. Pain corresponded to the side of the residual tube and pointed to obstruction at the fimbriated end in the remaining 40 cases, an incidence twice as great as obstruction at the uterine end.

Comparison of Insufflation With the Findings at Laparotomy and Lipiodol Examination.—An opportunity for comparing the insufflation findings of the residual tube with its anatomical status as found at laparotomy was afforded in 24 cases. In 7 cases the insufflation findings were compared to the results of a lipiodol examination. Time and space do not permit a detailed report in this paper. A few special cases may be mentioned.

Normal contractions and patency were demonstrated in one case by insufflation done before an operation for tubal pregnancy. At the laparotomy the uninvolved tube was somewhat swollen; the fimbriated end was open. No harm resulted from this insufflation; four months later this residual tube was found stenosed. In another case the tubes were insufflated in the presence of a tubal pregnancy two days before the laparotomy without causing untoward symptoms. The uninvolved tube appeared normal save for a few adhesions at the fimbriated end. Two insufflations, one sixteen days after operation and the other eleven weeks later, showed an obstructed residual tube. Twenty-seven months after the last insufflation, she developed a tubal pregnancy on the opposite side. The tube was found adherent to the ovary, the fimbriated end containing the impregnated ovum.

SUMMARY AND CONCLUSIONS

Ninety patients were examined by uterotubal insufflation to determine the status of the residual tube after an ectopic pregnancy. Seventy-seven patients came for the relief of sterility. Thirteen did not desire children. Sixteen patients were examined by uterotubal insufflation within two years after the ectopic pregnancy, and 74, later than two years. Eight patients had repeated ectopic pregnancy. Only 12.35 per cent of the 90 tubes were normally patent; 43.21 per cent were completely obstructed and 44.44 per cent were partially obstructed. Of the 23 untreated patients who became pregnant again after the tubal pregnancy, 7 proved to have normal tubal patency; and of the 67 untreated patients who did not become pregnant again, only 6 had normal tubal patency.

Of the 77 patients who desired to become pregnant again after a tubal pregnancy, 12 became pregnant after insufflation. Ten of the tubes showed some impairment of patency and function, and 2 were normal. Eight of these 12 patients had an intrauterine pregnancy, and 4 developed another tubal pregnancy. There appeared to be a definite relationship between the development of intrauterine and extrauterine gravidity on the one hand and the pressures encountered during the insufflation on the other. In general the pressures approaching 100 mm. Hg at uterotubal insufflation were followed by uterine pregnancy. The higher pressures (150-200 mm. Hg), indicating marked strictures, were followed by tubal pregnancy. Insufflation repeated once or several times may improve the tubal status and favor normal pregnancy.

Intrauterine pregnancy occurs with sufficient frequency after an operation for tubal pregnancy to encourage conservation of the residual tube. It occurs in spite of impairment in tubal patency.

In the surgical treatment of ectopic pregnancy, a distinction should be made between multiparous and nulliparous women. For the latter especially the following surgical rationale suggests itself:

A. When the patient's condition is serious, as little as possible should be done other than to insure the safety of the patient. The uninvolved tube should not be disturbed although it should always be inspected for the possibility of a coexistent tubal pregnancy. Inspection of the ovaries has similar importance. This rule applies to both parous and infertile women.

B. When the patient's condition is good, the uninvolved tube should be carefully scrutinized. If it is hopelessly diseased and the patient has borne a child, it should be removed. If only partialy impaired, it should be left in situ because intrauterine pregnancy occurs more often under such conditions than tubal pregnancy. The mere possibility of a second ectopic pregnancy is not an indication for salpingectomy. In any event

its pathologic status should be recorded as accurately as possible for the future.

C. Whenever possible, abnormal conditions should be corrected at operation. A salpingostomy or freeing of adhesions, or both, may be required. One of my patients, who bore a living child later, was thus treated. The age of the patient, her parity, and her desire to bear more children should influence and determine the procedure. In rare instances, a temporary ligation of the tube or some type of temporary sterilization is preferable to salpingectomy.

D. In cases of repeated ectopic pregnancy, when the patient is anxious to have a child and is willing to risk a third ectopic pregnancy, a partial salpingectomy may be performed with a plastic operation on the tube stump. The alternative of removing the gestation sac by simple incision and suture of the tube with or without curettement of the tube may be borne in mind. The feasibility and value of this procedure await future experience.

E. The early diagnosis of unruptured tubal gestation will make conservative operations on the pregnant and nonpregnant tube safer and more feasible.

REFERENCES

(1) *Schumann, E. A.:* Extrauterine Pregnancy, New York, 1921, D. Appleton & Co., pp. 161 and 102. (2) *Norris, C. C.:* Surg. Gynec. Obst. **58:** 741, 1934. (3) *Smith, R. R.:* Surg. Gynec. Obst. **18:** 684, 1914. (4) *Urdan, B. E.:* Am. J. Obst. & Gynec. **20:** 355, 1930. (5) *Brettauer, J., and Peterson, R.:* Quoted by Schumann.[1] (6) *Foskett, E.:* Am. J. Obst. **67:** 27, 1913. (7) *Rongy, A. J.:* Am. J. Obst. **77:** 86, 1918. (8) *Masson, J. C.:* Minnesota Med. **13:** 822, 1930. (9) *Lavell, T. E.:* Am. J. Obst. & Gynec. **18:** 379, 1929.

911 Park Avenue

Tassovatz: Resection of the Presacral Nerve in the Treatment of Dysmenorrhea, Bull. Soc. d'obst et de gynéc., p. 91, January, 1934.

The author reports five cases of dysmenorrhea treated by means of resection of the presacral nerve. No complications were observed in any of these cases. The menses continued to be regular and normal. There were no bladder or rectal disturbances or dyspareunia.

J. P. Greenhill.

Serdukoff and Soulimova: The Use of Avertin Anesthesia in Gynecology and Obstetrics, Gynécologie **32:** 529, 1933.

The authors consider avertin a highly satisfactory anesthetic in obstetrics and gynecology. It is a valuable hypnotic particularly in women with such severe complications as heart and pulmonary disease, in old age and hypertension where the usual forms of anesthesia are contraindicated. However, to obtain good results with avertin, it is necessary to control carefully the dose, and it is essential to prepare the reserve forces of the cardiovascular apparatus and such parenchymatous organs as liver, kidneys, heart, and lungs.

J. P. Greenhill.

CIRCUMCRESCENT AND CIRCUMVALLATE PLACENTAS

JAMES ROBERT GOODALL, M.D., MONTREAL, QUE.
(From the Royal Victoria Montreal Maternity Hospital and Department of Gynecology and Obstetrics, McGill University)

PLACENTAL circumcrescence is an outgrowth of placental villi beyond the boundaries of the chorionic plate. Circumvallation is an added complication to the former condition whereby there is "ditching" at the chorionic circumference. This complication occurs only in about 10 per cent of cases of circumcrescence.

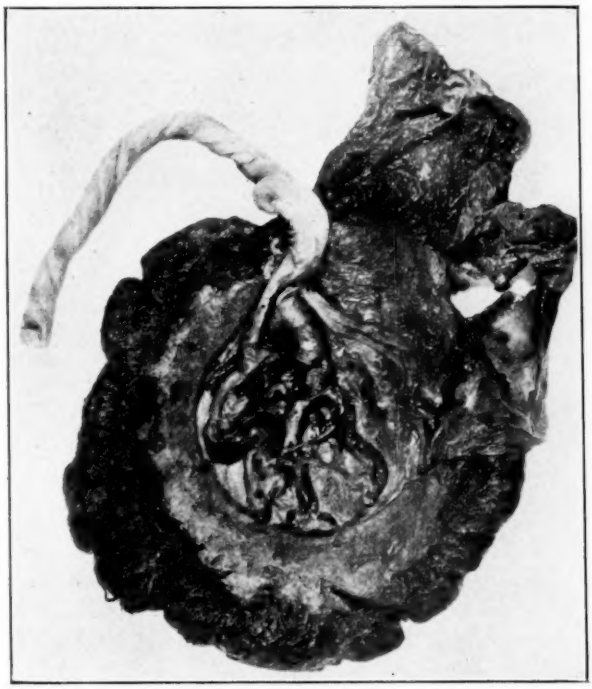


Fig. 1.—Concentric circumvallation.

Clinically, placental circumcrescence has a very fixed value, and anatomically the cases can be divided into two distinct, easily distinguishable groups: (1) concentric, and (2) eccentric or crescentic.

These two are similar in their mode of development but differ somewhat as to causation. The former, concentric circumcrescence, is a product chiefly of the first trimester of embryonic life; the latter, eccentric circumcrescence, of the second and third trimesters. Concentric circumcrescence takes at least two months to develop, after

the cause is in operation. The developmental period of eccentric circumcrescence is not definitely known, though probably of the same duration. Both types are an expression of compensatory hypertrophy.

METHODS

This work is based upon a critical examination of 750 placentas. The work will eventually comprise over 1000. The specimens were carded and immersed in 10 per cent formaline solution immediately after birth. They were all examined critically under running water, within a few hours (from eight to twenty-four) after immersion, and any abnormal characteristics were noted. They were then labeled with name and date and reimmersed in a fresh solution of formaline and preserved in jars for from four to six weeks. After a thorough rinsing, they were then sectioned in parallel slices, 1 cm. thick, by means of a large amputation knife on a block. These hardened slices were then critically studied with a large magnifying lens, and small blocks removed from any part that was of interest for microscopic study. The results have been startling and will be embodied in a monograph on placental pathology to appear within the year. This work will comprise several thousand slides in that from two to ten blocks were taken from each placenta.

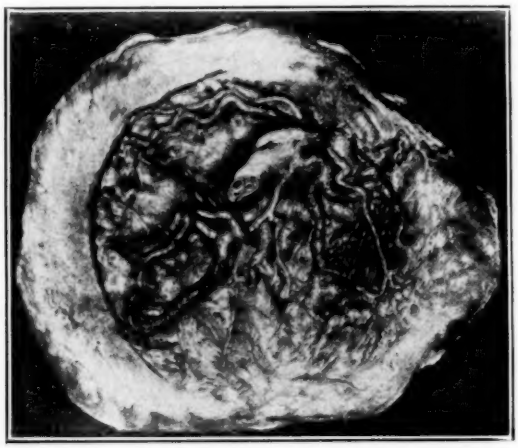


Fig. 2.—Eccentric circumcrescence.

MECHANISM OF PLACENTAL CIRCUMCRESCENCE

It would serve no useful purpose to review the history of research upon the circumvallate placenta. This was done so thoroughly by Dr. J. Whitridge Williams in 1929 that nothing could be clearer or more concise. In this work, Dr. Williams enumerated ten different theories, expressed his own criticism of each one, and finally elaborated his own, which was closely in concurrence with that of Meyer, 1909, who pointed out that the abnormality is the result of an originally too scanty development of the chorion frondosum. The fact that so many different views are held only goes to prove how imperfect is our knowledge of circumcrescence and circumvallation. In studying

the subject it will tend to clarity if we divide the work into three parts: I. The developmental relation of the chorion frondosum to the chorion laeve; II. The interrelation of the chorion frondosum and placental site; III. The relation of the chorion frondosum to uterine distension.

I. THE DEVELOPMENTAL RELATION OF THE CHORION FRONDOSUM TO THE CHORION LAEVE

At one stage of embryonic life, the whole embedded amniotic sac is covered with fluffy villi (Fig. 3). Later on, the growth of the villi becomes accentuated at a certain spot, usually situated proximal

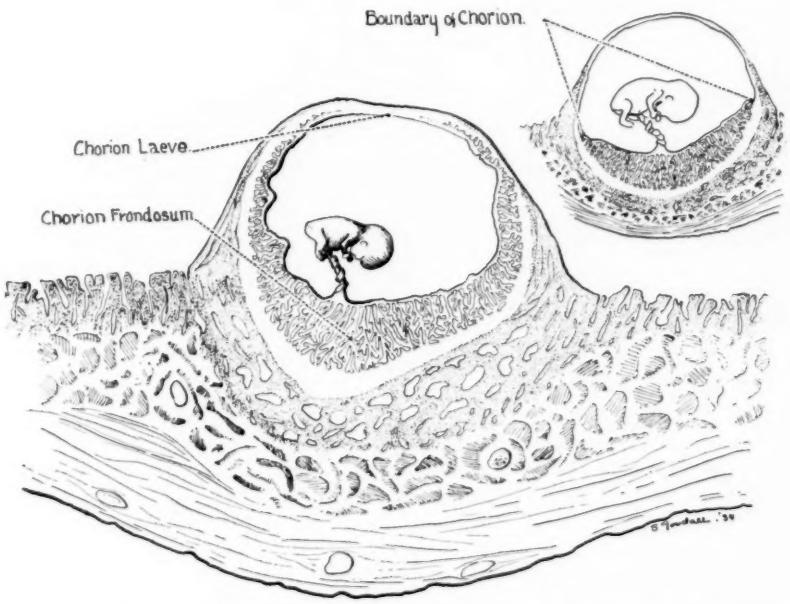


Fig. 3.—Diagram showing relation of chorion laeve and chorion frondosum.

to the uterine wall (Fig. 3, inset). This is the site of the future placenta and is spoken of as the "chorion frondosum" to distinguish it from the extra placental chorionic membrane, which is known as the "chorion laeve," upon which the villi atrophy. The fetal surface of the normal placenta is known as the placental plate and has very definite limits. The size of the placental plate is determined by many factors working either in collaboration or at cross purposes. First of all, it has been stated by one of the greatest authorities on embryology, that 50 per cent of the ova of the animal kingdom are defective. This may be inherent in the ovum before impregnation and may arise out of any one of many maternal causes, chiefly (1) endocrinologic, either hereditary or acquired, and (2) pelvic disease. To these may be added defects operating after impregnation and arising out of

diseases inherent in the uterine mucosa, which may also be primarily endocrinologic, or developmental (and therefore secondarily endocrinologic), or due to local or general constitutional diseases. These fetal and maternal factors working alone or in combination in early embryonic life determine the normal or abnormal activity of the trophoblastic layers, comprised of the syncitial and Langhans layers with their supporting mesoblastic framework. These, by their operation in early fetal life, determine the size of the chorionic plate, or chorion frondosum. It has been possible to demonstrate microscopically the widest divergent ranges of activity in these cells in different embryos of about the same clinical age—embryos removed therapeutically for maternal contraindications to the continuance of the pregnancy. These

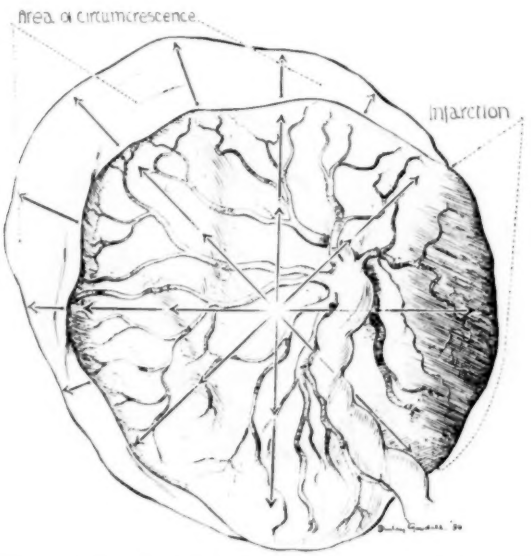


Fig. 4.—Lines indicating centrifugal growth of placenta.

specimens were therefore fresh and were hardened immediately upon removal. This same difference in trophoblastic activity was also noted independently by my colleague, Dr. J. P. Kearns. These factors, fetal and maternal, enumerated above, determine not only the size of the chorion frondosum, but also the possibility of the gestation reaching viability. When atrophy of the villi beyond the boundaries of the chorion has taken place, no matter what the needs of the fetus may be, regeneration of these can never occur. Once the relative dimensions of chorion frondosum and chorion laeve are fixed, they are fixed for all time. In other words, the limiting circumference of the chorionic plate becomes immutably set. In circumcrescence, though the subtended fronds may grow beyond the normal limits of the chorionic plate, their roots are always within the plate circumference.

Trophoblastic activity is an expression of the correlation of forces inherent in ovum, uterine bed, and nutrition. How like all other forms of life! They all find their determining characters in inheritance, soil, and food. Trophoblasts, acting under the foregoing influences, determine the size of the future placenta. Where all conditions are average and normal, the resultant placenta will be of average size. In oval dystrophy and maternal mucosal incompetence, a very large, poorly developed chorion frondosum may be the result, and *per contra*, when food supply and other conditions are in excess, the needs of the fetus may be adequated by a small, active, initial placenta. This excess of nutrition may be the expression of overactivity of the trophoblastic cells in producing excessive maternal periovular transudate, used by the fetus for its early nutrition. These are factors which determine the initial size of the chorion frondosum in relation to the laeve.

Other factors operating at a later date in pregnancy may change the initial characters of the placenta, but not its proportions relative to the chorion laeve.

II. THE INTERRELATION OF THE CHORION FRONDOSUM AND PLACENTAL SITE

The activity of the trophoblastic cells determines the relative initial sizes of the two chorions, the chorion frondosum and the chorion laeve. The distension and growth of the uterus determines in normal cases the degree of extension of both of these. Let us devote our attention exclusively to the chorionic plate, or chorion frondosum.

In normal cases the growth of the placental chorionic plate, after its initial size is determined by the agents already enumerated, depends upon the distension and growth of the uterus by its content. The juxtaposed placenta keeps pace in its growth with the placental site, which enlarges throughout pregnancy to reach at term an evolutionary size of that of a dinner plate. The growth of the uterus and placenta is not of equal pace throughout pregnancy. It varies at various stages of fetal evolution. The fetus does not reach its full growth until the full period of gestation has been spent. But it will be shown in the prospective monograph upon placental pathology that the placenta is a mushroom growth, of rapid and somewhat imperfect development, which obeys the laws of all life, in that it passes through its active childhood, its vigorous adolescence, reaches its quiescent balanced maturity, and passes into decadent senility. There is no such thing as a mature placenta at full term. They are all full of signs of old age. I have found only about 10 quasi-normal placentas at full term or at estimated full term. The others all presented various degrees of advanced senile and active disease pathology, and it will be one of the greatest problems in the forthcoming monograph to distinguish the changes due to senility, from those that are the result of

pregnancy intoxication and other diseases. It will not be opportune to enter deeply into the changes incident to placental pathology except to touch upon that which is germane to circumcrescence. Anything which interferes with the normal extensibility of the chorionic plate will prevent that placenta following with equal pace the growth of the uterine extension. The basic principle of normal interaction of placenta and placental site implies two equally healthy juxtaposed and adherent organs. Any disease of either upsets that normal balance of correlation. The greatest pathologic factor in upsetting that normal balance is chorionic sclerosis.

Chorionic sclerosis is one of the commonest, in fact the commonest, placental disease. It is, I think, an expression of placental senility, but like all senile decay it may be hastened by maternal and fetal disease. It is brought about always by a slow or rapid deposit of a clamping impediment—a deposit of edema and later fibrin tissue—chiefly about, but not confined exclusively to, the maternal decidual tissues and its accompanying blood vessels in and below the placental chorionic plate. Just as in human life senility may be very precocious, so may it be manifested in very early placental degeneration. It may occur in some placentas as early as the second and third month and is, I am inclined to think, evidence of an endocrine disturbance either in infant or mother or both. In eight whole placentas obtained through abortion at from the fourth to sixth month, exactly 50 per cent of them were markedly circumvallate with marked sclerosis, not only of the membranes and chorionic plate, but also in two cases a very decided scleroderma of the fetuses. Chorionic sclerosis of this type can be studied to best advantage in hardened specimens.

There is an additional sclerotic factor in the placental plate found in about 10 per cent of cases at term, less frequently in the earlier months of pregnancy. It is a perivascular exudate involving the fetal vessels, both arteries and veins, of the chorionic plate. This is at first an edema, reactionary to some unknown cause; later, the exuded plasma concentrates and appears like a thin layer of milk exuding from the vascular system between the mesoblastic layers of the chorionic plate. It may be well to point out that the mesoblastic tissues of the chorion are divided into two laminae, which can be easily separated, and between which the fetal vessels course before perforating the lowermost to invade the villous arborizations. The perivascular exudate described above, spreads ordinarily between the component layers of the chorion like a thin layer of milk oozing out of the blood vessels. But in many instances it may spread over the whole circumference of a part of any affected vessels, leaving the other portions of the fetal surface of the blood vessels unaffected. When this occurs there is usually a definite, easily perceptible narrowing of the vessel by the constricting exudate. Doubtless also the

involvement of vasa vasorum plays an important part in this vascular sclerosis, and spreading exudate. The important features arising out of this perivascular exudate are twofold. First, the spreading sclerosing substance between the chorionic layers and, second, the interference with normal nutrition of the chorionic plate by the diminished vascularization. The density of the chorion can be seen in its every phase as a sequence to this perivascular exudate. This type of sclerosis is best studied in the fresh placenta.

But one may ask, "How does sclerosis of the chorionic plate and its subjacent tissues produce circumcrescence?" By placing a restraint upon the centrifugal growth of the placenta in its endeavor to keep pace with the expanding placental site, which, in turn, is proportionate

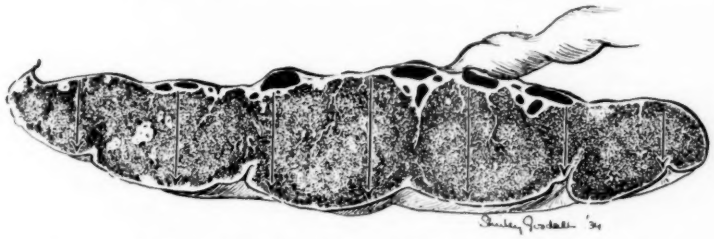


Fig. 5.—Normal placenta, showing direction of growth tension.

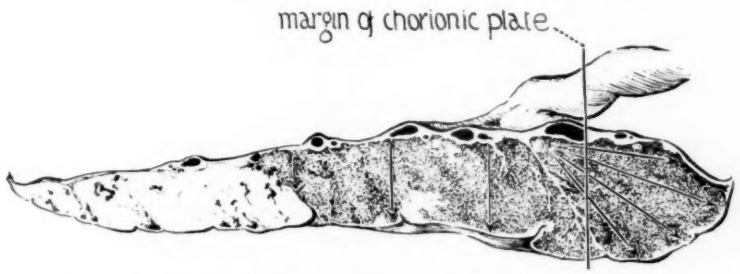


Fig. 6.—Infarcted placenta, showing compensatory hypertrophy lines of growth tension—eccentric circumcrescence.

to the whole uterine distension and growth. Normally the growth of the placental site and superimposed placenta is radial from a central point. These normally grow *pari passu*. But the impaired expansibility of a sclerosed chorion places an embargo upon its speed and vital activity, so that it can no longer keep pace with the evolutionary growth of the placental site. The centrifugal pull of the expanding placental site is exercised upon the chorionic plate, not only through the medium of the intervening anchoring villi, but also through the centrifugal circumferential pull of the chorion laeve in its endeavor to follow the growing uterus to which it is attached. But, if through sclerosis, the expansible properties of the chorion are below the normal, the villi will gradually respond to the centrifugal pull to the best of their ability, so that in a fully developed circumcrescence the pull

and hypertrophy cause the villi to extend their uterine ends beyond the area of the boundaries of the chorionic plate though their roots are always attached within the chorionic circumferential margin (Figs. 4, 6, 7, 8). Contrast the arrows of growth extension with the normal in Fig. 5.

The angle of villous growth therefore will not be directly downward at right angles to the chorionic plate, but will be at a more and more acute angle the farther one recedes radially from the central point of the placenta. In concentric circumcrescence this pull is equal in all radii. In eccentric circumcrescence the pull is radially unequal. This differene will require an explanation. In concentric circumcrescence, the process is usually slow, mild, and often manifests itself in the first half of gestation. The causative sclerosis is slow in

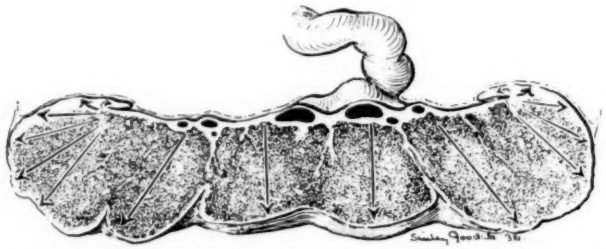


Fig. 7.—Concentric circumvallation, showing lines of growth tension and plication of chorion.

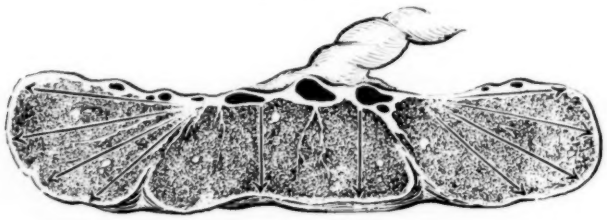


Fig. 8.—Concentric circumcrescence, showing lines of growth tension.

its development, relatively slight in degree, affecting chiefly the chorionic plate, but leaving the villi inappreciably altered. As the placental site expands *pari passu* with the general uterine growth, the chorion lags behind by virtue of its impediment. The villi follow the expanding site. The expansion is naturally greatest at the periphery. The resultant is an outstretching of the villi, attached fetally within the circumference of a relatively inexpansile chorion, and maternally to the expansile placental site. The disparity between the expansibility of the two villous attachments, and the duration of the imbalance will determine the degree of circumcrescence. Let us consider hypothetical cases. First, a mild degree of maternal or fetal disease produces a mild sclerosis of the chorion. The villi have not suffered appreciably. The imbalance between chorion and placental site will grow more marked as time goes on; compensatory hypertrophy of

the placental villi will take place manifested by increased thickness; and growth of the villi will be at gradually increasing obliquity from the placental margin to the circumference of the placental site. In these mild cases of long duration, circumcrescence may reach its greatest development, and it will always be concentric because the chorionic plate and its subtended villi will not have suffered at any one, more than at any other, part of its circumference. One may modify the intensity of the chorionic sclerosis to any degree imaginable, even to that of complete inexpansibility, and the response will be the same, though more rapid in its development. But one encounters in such cases a new factor that may modify the picture. In severe scleroses, the perforating fetal blood vessels may suffer much damage also and indirectly thereby affect the subtended villi, nutritionally and functionally, reducing compensatory villous hypertrophy almost to the inappreciable degree. Under these circumstances, there will be slight circumcrescence in a thin placenta incapable of hypertrophy. You may modify the component causative factors of concentric circumcrescence in intensity, duration, and period of gestation, and the effect will be a circumcrescence varying first, in degree; second, in concomitant villous hypertrophy, expressed in placental thickness; and third, in influence upon fetal growth and viability. The essential factor of concentric, as contrasted with eccentric circumcrescence, is to be found in the fact that at no part of the placental circumference have the villi been killed by the disease that affected the chorion.

Eccentric circumcrescence implies the death or greatly impaired vitality of a segment of the placenta, resulting in infarction and absorption of that area. The eccentric circumcrescence is nearly always greatest diametrically opposite the infarction in the placental area. Circumcrescence under these circumstances becomes again a compensatory development. Eccentric circumcrescence is usually the sequel to placental infarction and chorionic sclerosis. Concentric circumcrescence is a sequel to chorionic sclerosis alone. As infarction is rare in the first half of pregnancy, so also do we seldom find eccentric circumcrescence in the first five months of fetal life, except in cases of definite nephritis manifest in the early pregnancy months; which is relatively rare. On the contrary, we find mild grade of generalized chorionic sclerosis without villous infarction more commonly in the first semester of fetal life.

If chorionic sclerosis is the commonest placental disease at full term and is the chief causative agent of circumcrescence, why should circumcrescence be a relatively uncommon sequel? The answer is simple and satisfactory. Just as in cardiac or other organic disease, hypertrophy takes time to become appreciable, so we find that time is required in placental hypertrophy. It has been possible to estimate, in certain private cases, that it requires at least two months after the

cause has been in operation, for a circumcrescence to be appreciable. For this reason, sclerosis of the chorionic plate must necessarily begin before the end of the seventh month of gestation for circumcrescence to be appreciable at full term. Therefore, chorionic sclerosis is the commonest of placental degenerations. The very great majority of these cases are a late development of intrauterine life—too late to evoke hypertrophy and circumcrescence. Naturally sclerosis is relative in its degree of intensity, and inhibition to the extension of the chorionic plate is also relative. The history is often as follows: a more or less severe toxemic attack lasting two weeks or more in the early months of pregnancy, followed by natural immunity. Such a condition must occur before the end of the seventh month. If it occurs at a later date, it will produce merely a compensatory hypertrophy of the villi and a great thickening of the placenta, provided cell potentiality is such as to permit hypertrophy. It is probably not appreciated fully that quasi-normal placentas vary in thickness from 1 to 6 cm., the rough average being about 3 cm. If the sclerosis occurs slowly and uniformly and does not destroy or greatly affect the villous vitality, the villi will elongate universally, and will be pulled out at the margin of the placenta, causing the placental margins to be rounded and bulky, surpassing the boundaries of the chorionic plate; under these circumstances the circumcrescence will be concentric because at no part of the margin have the villi been destroyed. But the story is a different one in the case of an eccentric circumcrescence. In these cases, when the flood of disease that caused the chorionic sclerosis has passed over the placenta, it also left an universal disease of all the placental parenchyma in which certain parts of the placenta were more severely affected than others. Consequently some villous portions involving a segment of the placenta and its subtended circumference succumb to the acute or subacute process, whereas parts more remote suffer less and are regenerated or suffer apparently not at all. Usually the farther one recedes diametrically across the placenta from the affected area, the less is the effect of the blight apparent. On cross-section of such a placenta one sees the diseased margin is thin and fibrous, and under the microscope one finds that the villi will have undergone cloudy swelling and fatty degeneration and absorption, leaving the more resistant maternal fibrin-laden tissues in an advanced state of hyaline degeneration, often with cavitation. As one looks back from this highly degenerated area, the placental tissues are found in lesser degrees of destruction; some function is still retained, though the inherent cell potentiality is usually so low as to permit only precarious survival, but not hypertrophy. As one looks back still further, potential cell power increases so that not only is repair of damage possible, but hypertrophy to compensate both for the lost function in the diseased portion and for meeting the increas-

ing demands of fetal growth may also be possible. This compensatory hypertrophy is beautifully illustrated in Fig. 6, which represents the usual condition in cases of eccentric circumcrescence. The hypertrophy which first precedes, and then goes on *pari passu* with the circumcrescence, is also detectable in the great length of the fronds in the circumcrescent area. In the normal placenta, the fronds gradually grow shorter as one approaches the chorionic margin, therefore in marked contrast to the long hypertrophic marginal fronds of the circumcrescent placenta. Contrast Fig. 5 with Figs. 6, 7, and 8, in which it is shown that in the area of compensatory hypertrophy, the fronds become of extreme length and divergence. It is a noteworthy fact brought to my attention by my colleague, Dr. John Fraser, that an attack of acute placentosis, which may, of course, be of any degree of acuteness, produces less destruction in the growing and mature placenta than an attack of similar intensity would produce in the decadent stage of placental senility. It therefore follows that concentric circumcrescence is more common in the earlier fetal months because the resultant temporary blight usually leaves no trace of its passage except a stiffening of the supporting structures, and the regenerative forces of fetal tissues in the full vigor of their adolescence permit a restoration which could not be expected in the stage of decadent placental senility. It therefore follows also that eccentric circumcrescent hypertrophies preponderate over the concentric type because of the foregoing two factors, (1) the greater incidence of toxemia in the later months of pregnancy, and (2) their greater destructive power in placental senility, at which stage not only is there sclerosis of the chorionic plate, but also partial or complete atrophy of a segment of placental fronds. But what is "placentosis"? It is a new name for one of the commonest of placental diseases; it is the precursory stage of white infarctions; quick in its manifestation, varying in its intensity, selective in its incidence, and transitory in action; susceptible of repair if not too intense, and deadly to both placenta and child if intensive and diffuse; often subacute and creeping in placentas showing all stages of simultaneous repair and destruction; affecting not only one-half of a placenta to the degree of total atrophy, leaving the other half less affected and capable of carrying on, but also affecting to a marked degree one placenta of a twin pregnancy so as to place the attached child's life in jeopardy, yet leaving the other but slightly disturbed. This and other diseased conditions must be left to be dealt with fully in a subsequent work. It is this placentosis which operates with so much more destructive effect upon the senile placenta, in marked contrast to the lesser changes in younger placental elements.

The question arises at once, "Why should a placenta which has not fulfilled its complete function become senile from the seventh month

on, when the fetus must still grow and its demands must be met?'' There are many reasons for this. First, senility is a relative term. A man, fifty years old, has a greater capacity for certain types of work and lessened capacity for other kinds of labor than when younger, yet his biology will undoubtedly register signs of senile decadence. But it is work of a different kind that is demanded of such. So it is with the placenta. The average concept of the placenta is that its only function is to bring oxygen and food and take away catabolic elements and that therefore the demands upon the placenta should increase with the growth of the fetus. This is but a superficial view of the situation. In the early stages of fetal life, cell activity is estimated by physiologists to be twenty-five times that of the human adult; it is also estimated that the rate of cell division and metabolism slow down gradually as fetal maturity is approached. Fetal life is like terrestrial life, it progresses from its embryologic stage to its maturity at term. It would be unorthodox to expect the young boy's metabolism in the old man. But of far greater significance are the other properties of the placenta which center chiefly in its capacity as a storehouse for the elements necessary for the growth of the fetus, such as endocrines, glycogen, etc.—elements which the fetus is incapable of generating in its anaplastic state, but which generation it gradually assumes for itself as it reaches maturity. May I make this very clear by just one example. An animal whose pancreas is excised will die very quickly from glycogenic disturbance due to the withdrawal of the pancreatic endocrine. If the same operation is performed upon another animal in the early stages of pregnancy, the result will be the same. But a similar operation upon an animal in the late stages of pregnancy will have no appreciable effect upon the mother during the duration of the pregnancy, but she will die promptly after delivery. There is but one interpretation, and that is that the fetuses take over their own functions at the proper time and, in case of need, may even supply a deficiency in the mother. It is doubtless the assumption of functions by the fetus at different stages of its development that makes an early large placental reserve unnecessary in the later months of gestation. Moreover, need I mention that the placenta, like every other form of living thing, has its own life history, and is not exempted from senility? And among placentas there are the averages, and the prematurely senile, and the retarded decadences, just as in humans.

III. THE RELATION OF THE CHORION FRONDOSUM TO UTERINE GROWTH AND DISTENTION

Just as the trophoblasts determine the initial size of the chorionic plate in relation to the chorion laeve, so there are factors later in pregnancy which determine the relation in size and thickness of the

placenta to the size of the uterine content. The normal placenta grows *pari passu* with the growth of the placental site, and this latter is proportionate in its extension to the uterine distention. Factors such as hydramnios, acute or chronic, may cause a marked extension of the placental site, in keeping with the increase in the uterine content, and if the chorionic plate is sufficiently elastic to keep pace with the rapid extension of the placental site, the placental thickness will become correspondingly reduced. In the same manner a gradual reduction in the uterine content will have a corresponding effect in reducing the placental site and with it the circumference of the placenta, causing an increase in the thickness and compactness. This reduction reaches its acme of rapidity and degree in the retraction after birth of the child. The placental site so reduces itself that the placenta follows it for a time by increasing its thickness and compactness, but its elasticity relative to that of the tissues underlying the placental site causes a "buckling," which is the first stage of placental separation.

So it becomes evident that through the trophoblastic agencies the initial relation between the chorion frondosum and chorion laeve is fixed; that uterine growth and distention determine the relation of placental site to uterine content; and expansibility or sclerosis of the chorionic plate determines the relation of placenta to placental site.

Circumvallation.—Circumvallation is an added complication to an hypertrophic circumcrescence. Circumcrescence must always precede circumvallation. As the name implies, it means a "ditching" at the margin of the placenta and an apparent or real cupping of the placental plate so that it presents a concave instead of a convex surface toward the fetus. This concavity is most marked in the early fetal concentric hypertrophies and is best illustrated in nature by the growth of a mushroom or toadstool. In the case of the toadstool or fungus, the smooth upper surface corresponds to the chorionic plate, and the undergrowth of plates corresponds to the placental fronds. If weather conditions are normal, the upper and under surfaces keep pace in their growth. If there is too much moisture the "fronds" grow too rapidly and split the "chorion." This, of course, cannot occur in the placenta. But, if the atmosphere is too desiccating, it dries the upper surface of the fungus, and to accommodate the progressive undergrowth with which it cannot keep pace, owing to its desiccated sclerosis, it cups and presents a concavity instead of a convexity to the surface. The similarity to the placental stages is very striking. But there is an additional factor to explain the "ditching" at the margin of the chorionic plate. This "ditching" or circumvallation may be concentric or eccentric, depending upon whether the case was previously of the one or the other type. But "ditching" need not involve the whole circumference of the placenta even in a case of concentric hypertrophy, nor for that matter need it involve the whole of

the segment of the placenta showing eccentric hypertrophy. The vagaries of circumvallation are many. In a few cases there may be numerous circumvallations concentric with the major one at the margin of the chorion plate. These minor ones may be as numerous as six, merely duplications of the surface layer of the chorion. Circumvallation is the late result of a reactionary edema expressive of a fetal outpouring of lymph as a diluent to the maternal fibrin-laden tissues, behind which is probably a maternal toxemia. This edema lies under the amnion and invades the layers of the chorion. The amnion is usually raised by the fetal fluid from its attachment to the chorion. The chorion is made up of two or more distinct but firmly adherent layers,

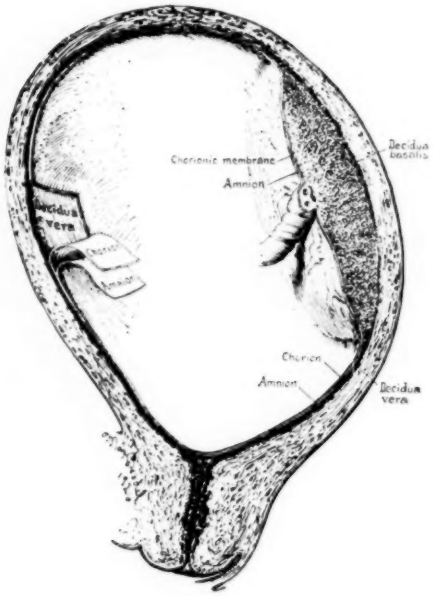


Fig. 9.

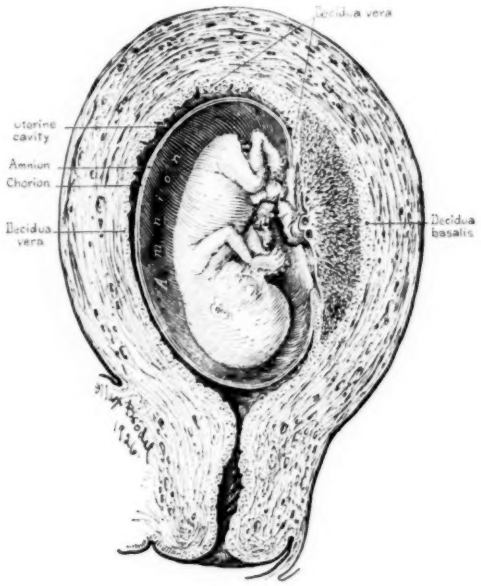


Fig. 10.

between which the larger fetal vessels run before they perforate the subjacent cribriform plate to become the main stem and support of the fetal fronds. The edema is most marked where the maternal decidual tissue is in greatest quantity and is undergoing degenerative changes. Decidual tissue is most abundant in the placental area on the surface of the circumcrescence and is most liable to degeneration because it has been raised from its natural maternal bed and, as a consequence, is further removed from its blood supply. No matter what the degree of circumcrescence, fibrinosis of greater or less degree marks the boundaries of the chorionic plate. Consequently it is at this spot that the edematous reaction is most marked, and plication takes place, single or multiple, of the loose chorion, superimposed upon the circumcrescent surface. (Contrast Figs. 9 and 10.) It is a property of pla-

cental edema that it soon changes its physical characters and becomes a residuum of fibrin tissue which gradually solidifies and contracts, thereby adding greatly to the sclerosis of the chorion plate. In the early stages it is flocculent and easily torn. In the older stages, where circumvallation has taken place, the fibrinosis may take on great density and a ropelike strength. I have excised this circumvallate ring in many cases, and find that the ring alone will frequently sustain a pull of from 5 to 15 pounds, depending not so much upon the thickness of the circumvallate cord as upon its duration and consequent change from fibrin to fibrosis. The larger placental vessels always dip through the chorion within the ring of circumvallation, to pursue a centrifugal radial direction to feed the fronds in the hypertrophic circumcrescence.

Clinical Significance of Circumcrescence and Circumvallation.—J. Whitridge Williams stated in his concluding remarks in this work in 1929 that circumvallation had no clinical significance. Schumann, writing in the *Curtis System of Gynecology and Obstetrics* also wrote as follows: "This anatomical anomaly has no clinical significance except in its occasional association with widespread placental infarction."

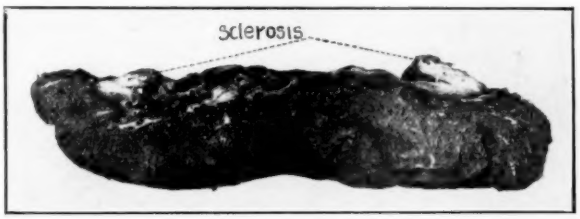


Fig. 11.—Sclerosis of circumvallation.

From what has already been written it can readily be seen that this statement is not correct—either in its conception of the association of two diseases or in its appreciation of the clinical significance. First of all, the two conditions, circumvallation (and therefore circumcrescence) and "widespread placental infarction," are not mere "occasional associations." They lie in the relationship of cause and effect. The "widespread infarction" means that a storm has passed over the placenta and that a large portion of the placenta is placed *hors de combat* by the resulting infarction; the compensatory hypertrophy and circumcrescence is an expression on the part of the placenta to keep up its reserve and preserve the life of the fetus. These then operate not as accidentally associated diseases, but as cause and effect, and the sclerosis of the chorion, as a resultant of the storm, restricts the expansibility of the chorion, preventing its keeping pace with the compensatory villous hypertrophy. Chorionic sclerosis may vary in its intensity and inhibitory effect from, let us say, 5 to 100 per cent. In the minor types villous compensatory hypertrophy will not be appreciably in-

hibited, and the chorionic defect can be made up entirely by the hypertrophy. Placentas vary from 1 cm. to 6 cm. in thickness. The thinner types are usually the result of atrophy; the thicker ones, of hypertrophy. Circumcrescence is always associated with hypertrophied villi, longer and more arborescent; unless, subsequent to the compensatory circumcrescence, the placentas are overtaken by another attack of destructive agencies. Its clinical significance can be best judged by a careful examination of all cases of hypertrophy. Naturally in the majority of circumcrescent placentas cases with birth at term, there will not be any appreciable effect upon the size or growth of the child because the hypertrophy will have compensated for the diseased area of the placenta and placental reserve may not be appreciably lowered; and therefore, the fetal nutrition may have suffered but slightly, or not at all. That is the history in most instances of birth at term. But the clinical significance is quite another story when we are dealing with concentric circumcrescence of the early months of fetal life. Here the restriction of the extensibility of the chorionic plate places a limit to the villous hypertrophy and circumcrescence, and though these two factors may keep pace with the fetal growth for a time, there will come a period when the placental growth cannot meet the demands. This disparity will increase with the weeks and eventually a macerated, emaciated fetus is cast off, or a sclerosed, emaciated octogenarian is born, which survives if it is old enough. It all resolves itself into a question of:

1. The time of the placental disease in the period of gestation
2. The intensity and duration of the causes which affect the placenta
3. The extent of the damage
4. The recuperative cell power (potentiality) of the surviving placental villi
5. The degree of restraint placed upon the chorionic elasticity by the resultant chorionic sclerosis.

It has been clearly shown by Kearns that whereas it requires a certain length of time and a certain pressure to force a glutinous substance through the vessels of a normal placenta, in placentas in which there are large infarctions, much less time and a much reduced pressure are required to force the same fluid through the compensatory hypertrophied portion. This shows that the fetal circulation is accelerated through the compensating area, either by vasomotor dilatation or by development of new and large vessels; that vascular exchange between mother and fetus is correspondingly hastened, and that this placental nutrition is heightened permitting increased cell activity and power of villous restoration.

1472 Sherbrooke Street.

SARCOMA OF THE UTERUS

Factors Influencing the Results of Treatment

Robert A. Kimbrough, Jr., M.D., Philadelphia, Pa.

THE literature on sarcoma of the uterus consists chiefly of reports of isolated cases and discussions dealing with its histogenesis, gross pathology, and histologic characteristics. Data on end-results are meager and incomplete; a careful search of the literature failed to disclose a single report of five-year results in a group sufficiently large to warrant conclusions, and, with the possible exception of one or two contributions, the same applies to data on three-year results.

Knott[8] reviewed 118 collected cases; results were not stated in 20; "recovery" following hysterectomy was noted in 31 of the remaining 98, but, in many, only a few months had elapsed since operation.

Miller[10] collected 180 cases treated by hysterectomy; only 12.7 per cent of these were reported free from recurrence one year after operation.

Proper and Simpson[11] reported 22 cases of malignant myoma and stated that 40.9 per cent were free from recurrence at intervals varying from six months to three years after treatment.

Evans[2] reporting 72 cases of "malignant myoma" from the Mayo Clinic found 61 patients (84.7 per cent) free from recurrence for periods ranging from four months to fourteen years after operation. His follow-up data, however, were incomplete, and untraced patients were assumed to be well.

Masson[9] reported 50 cases of sarcomatous degeneration of myomata from the Mayo Clinic and stated that 72 per cent were in good health three or more years after treatment.

Steinhardt[14] reported 38 cases, only 18 of which were operable. Ten of these were free from recurrence at intervals of one to six years after operation. Eight patients had remained well longer than six years postoperatively.

Unbehaun[15] reported 12 cases; 9 patients of this group were living and well from a few months to nine years after hysterectomy. Eight had received postoperative roentgen ray therapy.

Seitz and Wintz[13] reported the results of roentgen ray therapy in a series of 22 inoperable cases; 4 of the 8 patients who were treated more than three years prior to the report were free from recurrence. Ten had been treated less than two years previously, and all of these had responded well to treatment. Steinhardt, on the other hand, found the Seitz and Wintz technic of no value in the treatment of four inoperable cases.

Regaud and Lacassagne[12] recorded the results of irradiation therapy in 6 inoperable cases of sarcoma; 5 patients died within six months and one remained well three and one-half years after treatment. Beclere[1] cited 9 cases from the literature in which recurrence had not developed for periods of from two to seven years following irradiation therapy.

Numerous additional writers record the long survival of individual patients who have been operated upon for uterine sarcoma. Little of the data from the literature, however, can be utilized in determining prognosis since the five-year criterion of cure is so rarely observed in the presentation of statistics.

The present analysis is based upon 43 cases of sarcoma of the uterus in the department of gynecology of the Hospital of the University of Pennsylvania from 1900 to 1933. The study was undertaken in an effort to determine the factors which influence the end-results.

INCIDENCE

During this period 1,306 cases of carcinoma of the uterus were admitted to the department; sarcomas, therefore, constitute 3.2 per cent of uterine malignancies. This relationship of 1 sarcoma to 30 carcinomas is in accord with previously reported statistics; Veit[16] found the proportion to be 1 to 37; Evans, 1 to 40; Frankl,[4] 1 to 27; and Frank,[3] 1 to 30 or 40.

Although accurate differentiation between primary and secondary growths constitutes a difficult problem and is, to a certain extent, arbitrary, 17 of the 43 cases were classified as primary. The criteria for the diagnosis of primary tumors were absence of other myomas and absence of gross or histologic evidences of a preexisting myoma at the site of the sarcoma. In the remaining 26 cases, malignancy had developed in myomas. During the period covered by this study, 3,388 patients were treated for uterine myomas (Table I). Twenty-five hundred fifty of these patients were operated upon, and the incidence of sarcomatous degeneration was 1.02 per cent. Irradiation therapy was employed in 838 patients. The subsequent course is known in approximately 92 per cent of these and none has developed sarcoma. The incidence of sarcomatous degeneration in the entire series is 0.76 per cent, which is identical with that in 91,310 cases of myoma collected from the literature (Table II).

TABLE I. SARCOMATOUS DEGENERATION OF MYOMAS

MYOMA CASES TREATED	NUMBER	SARCOMATOUS DEGENERATION	
		NUMBER	PERCENTAGE
In our clinic	3,388	26	0.76
(a) Operated	2,550	26	1.02
(b) Irradiated	838	0	0.00
Collected from literature	91,310	701	0.76

The ages of the patients varied between twenty-two and sixty-seven years, the average being forty-seven (Table III). The highest incidence occurred in the sixth decade. One-half of the patients were above the age of fifty years, and in this group, with but one exception, the sarcomas developed after establishment of the menopause.

The choice of supravaginal hysterectomy or myomectomy (Table IV) rather than total removal of the uterus is explained by failure to make the diagnosis of sarcoma at the time of operation. Because of contraindications to operation, radium alone was employed in 3 cases. In 4, the lesions were so far advanced as to preclude any form of treatment.

TABLE II. INCIDENCE OF SARCOMATOUS DEGENERATION OF MYOMAS (FROM LITERATURE)

AUTHOR	NO. CASES OF MYOMA UTERI	NO. CASES OF SARCOMA	INCIDENCE OF SARCOMA
Steinhardt	1,363	38	2.78
Unbehaun	356	12	3.40
Haase[6]	710	30	4.20
Frankl	1,878	38	2.02
Imhauser[7]	208	11	5.28
Proper and Simpson	357	22	6.16
Masson	4,322	44	1.01
Miller (collected)	9,750	191	1.96
Geist[5]	250	12	4.80
Vogt[17] (collected)	72,116	303	0.41
Totals	91,310	701	0.76
Present Series	3,388	26	0.76

TABLE III. SARCOMA OF UTERUS—AGES OF PATIENTS (43 CASES)

AGES	PATIENTS	
	NUMBER	PERCENTAGE
20 to 49	20	46.5
50 to 69	21	48.8
Not stated	2	4.7

TABLE IV. SARCOMA OF UTERUS—TREATMENT (43 CASES)

TYPE OF TREATMENT	NUMBER OF CASES
Supravaginal hysterectomy	21
Total hysterectomy	13
Radium	3
Myomectomy (abdominal)	2
Not treated	4

Operation was supplemented by irradiation in 8 cases; in 4, irradiation was used in treatment of postoperative recurrences; in 3, after incomplete excision of the growth; in the remaining case, treatment was given as a prophylactic measure after apparently complete excision of a sarcomatous myoma. This patient has remained well for eleven years, and one who was treated for recurrence presents no evidence of sarcoma six years after treatment.

There were no immediate deaths following the use of radium or diagnostic curettage. Four of the 36 patients subjected to operation died in the hospital; 2, of peritonitis on the eighth and thirtieth days, respectively; one, of sepsis on the eighth day; and one, of shock

within the first twenty-four hours. The immediate mortality in the entire group was 9.3 per cent and in the operative cases was 11.1 per cent.

Thirty-five of the 43 patients were treated more than five years ago (Table V). In evaluating the results, only those who are living and

TABLE V. SARCOMA OF UTERUS—END-RESULTS

		PATIENTS	
		NUMBER	PERCENTAGE
Treated 5 or more years ago		35	100.0
Alive and well 5 or more years		12	34.3
Operative mortality		4	11.4
Died of Sarcoma		19	54.3
Within 6 months	7		
6 to 12 months	2		
1 to 2 years	3		
2 to 3 years	1		
3 to 4 years	1		
8 years	1		
25 years	1		
Not traced (dead?)	3		

free from recurrence five or more years after operation are considered as cured. The 3 untraced patients are counted as having died of sarcoma. On this basis, the total salvage is 34.3 per cent.

Forty-seven per cent of those who died of sarcoma lived less than twelve months after operation. The longest interval between operation and the appearance of recurrence was fourteen years; although this patient died of sarcoma, her life was prolonged eleven years by irradiation therapy.

TABLE VI. FIVE-YEAR END-RESULTS—INFLUENCE OF COMPLETE VERSUS INCOMPLETE OPERATION

(DATA AVAILABLE IN 29 CASES)

OPERATION	PATIENTS TREATED FIVE OR MORE YEARS AGO		
	NUMBER	CURED	PERCENTAGE CURED
Complete excision	20	10	50.0
Incomplete excision	9	1*	11.1

*Myomectomy.

Complete excision of the growth was apparently accomplished in 20 patients, 10 of whom are living and present no evidence of recurrence for periods ranging from five to thirty-two years (Table VI).

Obviously there is little chance of operative cure unless the sarcoma be completely removed. In 9 cases, excision was not complete. In one, sarcoma was present in a myoma which had been removed by abdominal myomectomy. Microscopic study revealed that the capsule of the tumor was penetrated in several areas; yet this patient was

well and free from recurrence ten years later. Such a result is in favor of the contention that histologic evidence of malignancy does not invariably signify clinical malignancy.

Evidence of the higher degree of malignancy of primary sarcoma as compared to sarcomatous degeneration of myomas is shown in Table VII. These results clearly indicate that the prognosis in secondary tumors is at least three times more favorable than in the primary group. A possible explanation of this fact will be considered later.

TABLE VII. FIVE-YEAR END-RESULTS—INFLUENCE OF PRIMARY VERSUS SECONDARY SARCOMA
(DATA AVAILABLE IN 32 CASES)

SARCOMA	PATIENTS TREATED FIVE OR MORE YEARS AGO		
	NUMBER	CURED	PERCENTAGE CURED
Primary	13	2	15.3
Secondary	19	10	52.6

TABLE VIII. FIVE-YEAR END-RESULTS—INFLUENCE OF TREATMENT BEFORE AND AFTER MENOPAUSE
(DATA AVAILABLE IN 29 CASES)

TIME OF TREATMENT	PATIENTS TREATED FIVE OR MORE YEARS AGO		
	NUMBER	CURED	PERCENTAGE CURED
Before menopause	12	8	66.6
After menopause	17	3	17.6

TABLE IX.—FIVE-YEAR END-RESULTS—INFLUENCE OF LOCATION OF TUMOR
(DATA AVAILABLE IN 32 CASES)

LOCATION	PATIENTS TREATED FIVE OR MORE YEARS AGO		
	NUMBER	CURED	PERCENTAGE CURED
Submucous and endometrial	21	7	33.3
Subperitoneal	5	2	40.0
Intramural	6	3	50.0

Age also seems to be of prognostic import. Table VIII shows a five-year cure in two-thirds of the premenopausal group and in only one-fifth of those who had passed the menopause.

It is interesting to note that the tumors were primary in 75 per cent of the postmenopausal group and in only 10 per cent of the younger women. It seems likely that the higher incidence of primary sarcomas after the menopause may account for the lower cure rate in the older group.

The lower curability of the submucous and endometrial sarcomas is probably attributable to the high incidence of primary tumors in this

location (Table IX). On the other hand, 9 of the 11 mural and subperitoneal sarcomatous growths were found in myomas, and their secondary development may account for the better end-results in these groups.

The histologic type of the tumor has a definite bearing on prognosis (Table X). Of the three most common types, a far greater salvage

TABLE X.—FIVE-YEAR END-RESULTS—INFLUENCE OF HISTOLOGIC TYPE OF SARCOMA (DATA AVAILABLE IN 27 CASES)

TYPE	PATIENTS TREATED FIVE OR MORE YEARS AGO		
	NUMBER	CURED	PERCENTAGE CURED
Spindle	10	7	70.0
Small round	8	2	25.0
Polymorphous	6	1	16.6
Carcinosarcoma	2	0	0.0
Large round	1	1	100.0

can be anticipated in tumors exhibiting the more highly differentiated cellular morphology which characterizes the spindle-celled group. A striking decrease in salvage occurred in the relatively anaplastic small round cell and polymorphous sarcomas. The rare and highly malignant carcinosarcoma was found in two patients both of whom died a few months after operation.

For obvious reasons, the 3 untraced cases and the 4 operative deaths have been excluded in evaluating the influence of cellular morphology on the end-results.

MITOSIS AS AN INDEX OF MALIGNANCY

From a study of 72 cases of malignant myoma, Evans concluded that the number of mitotic figures bears a direct relationship to the degree of malignancy. Using an ingenious plan for estimating the number of mitoses in 1 cm. of tumor tissue,* he found only 2 patients living out of 13 whose tumors presented from 2,200 to 12,000 mitotic figures in each cubic millimeter; there were no recurrences after operation in a group of 11 patients whose tumors showed from 200 to 800 mitoses; 48 tumors showed either no mitotic figures or only an occasional one and none of these recurred after removal. Proper and Simpson, in an earlier paper, also emphasized the prognostic value of estimating the number of mitoses.

In the present series, satisfactory tissue was available for counting mitotic figures in 39 cases. In 2 of these no figures were found; the

*"The computation to determine the number of mitotic figures in a cubic millimeter of tumor tissue: Diameter of oil immersion field—0.170 mm.; radius—0.085 mm.; area of one field—(3.1416 times the square of the radius) 0.022698 sq. mm. Taking the average thickness of section as 0.011, the cubic contents of one microscopic field would be 0.000249678 cm. or approximately 0.00025 cm., or 1/4000 of a cm. Therefore, having determined the number of mitotic figures in 100 fields, the number in a cubic millimeter would be 4,000 times the average number in one field or 40 times the number in 100 fields."—Quoted from Evans.

counts in the remainder ranged from 80 to 7,160 per cubic millimeter. No tumors presented counts between 880 and 1,120 and this gap was selected as the dividing point between "low" and "high" counts.

As previously stated, primary sarcomas proved clinically to be about three times as malignant as sarcomatous degenerations of myomas.

If the number of mitotic figures is an index of the degree of malignancy, the primary tumors should show a greater number than the secondary. With this object in view, the number of mitoses was estimated in the two groups; the primary tumors showed an average of 1,889 figures as compared with 1,045 in the secondary group. These findings coincide with the clinical evidence and tend to prove the value of the mitotic figure content as an index of the degree of malignancy.

Table XI shows the incidence of recurrence in relation to the number of mitoses. Recurrences were more than twice as frequent in the tumors showing a high mitotic figure count.

TABLE XI.—INCIDENCE OF RECURRENCE IN RELATION TO DEGREE OF MALIGNANCY
(DATA AVAILABLE IN 34 CASES)

MITOTIC FIGURES PER CM. OF TUMOR TISSUE	NUMBER OF CASES	RECURRENCES (EARLY OR LATE)	
		NUMBER	PERCENTAGE
0- 880	20	8	40.0
1,120-7,160	14	13	92.8

TABLE XII. FIVE-YEAR END-RESULTS—INFLUENCE OF DEGREE OF MALIGNANCY IN CASES TREATED BY OPERATION ALONE
(DATA AVAILABLE IN 25 CASES)

MITOTIC FIGURES PER CM. OF TUMOR TISSUE	PATIENTS TREATED FIVE OR MORE YEARS AGO		
	NUMBER	CURED	PERCENTAGE CURED
0- 880	17	8	47.0
1,280-4,280	8	1	12.5

TABLE XIII. RESULTS OF IRRADIATION THERAPY—INFLUENCE OF DEGREE OF MALIGNANCY
(DATA AVAILABLE IN 10 CASES)

MITOTIC FIGURES PER CM. OF TUMOR TISSUE	PATIENTS IRRADIATED		
	NUMBER	CURED	PERCENTAGE CURED
200- 400	3	0	0.0
1,120-7,160	7	2	28.5

The prognostic value of the mitotic figure count in patients treated by operation alone is shown in Table XII. The percentage of five-year cures in tumors presenting low counts is practically four times as great as in those showing high counts.

A similar study (Table XIII) was made of 10 tumors treated by irradiation, either alone or for postoperative recurrences, to determine the value of the mitotic figure count as an index of radiosensitivity. This group is much too small to justify conclusions but the fact that the only cures were in the high count group suggests that there may be a direct relationship between the number of mitotic figures and the response to irradiation therapy.

SUMMARY

The literature dealing with the results of treatment of sarcoma of the uterus is reviewed.

A group of 43 cases of sarcoma of the uterus is analyzed from the standpoints of age, treatment, and factors which may influence the end-results.

The incidence of sarcomatous degeneration in our series of myomas, as well as in cases collected from the literature, was 0.76 per cent.

The total five-year salvage was 34.3 per cent.

The five-year salvage in 20 operable cases was 50 per cent.

Prognosis in sarcomatous degeneration of a myoma is three times more favorable than in primary sarcoma.

The salvage in younger women is more than three times as great as in women who have passed the menopause.

Small round cell and polymorphous tumors are more highly malignant than the spindle-celled type.

Recurrences after operation were more than twice as frequent in a group of tumors presenting a large number of mitotic figures as in tumors with relatively lower counts. Conversely, the five-year salvage was almost four times as great in the low count groups as in the tumors showing more numerous mitoses. Although in final analysis the presence of mitoses indicates nothing more than rapid growth, these results seem to justify the conclusions that the estimated number of mitotic figures is a reliable gauge of the degree of malignancy and is of distinct value in prognosis.

REFERENCES

(1) *Beclere, A.:* Strahlentherapie **38:** 113, 1930. (2) *Evans, N.:* Surg. Gynec. Obst. **30:** 225, 1920. (3) *Frank, R.:* Gynecological and Obstetrical Pathology, Philadelphia, 1931, D. Appleton-Century Co., p. 231. (4) *Frankl, O.:* Arch. f. Gynäk. **124:** 67, 1925. (5) *Geist, S. H.:* Am. J. Obst. **69:** 766, 1914. (6) *Haase, W.:* Ztschr. f. Geburtsh. u. Gynäk. **102:** 344, 1932. (7) *Imhauser, K.:* Arch. f. Gynäk. **123:** 12, 1924. (8) *Knott, Van B.:* Ann. Surg. **33:** 137, 1901. (9) *Masson, J. C.:* Am. J. Obst. & Gynec. **5:** 345, 1923. (10) *Miller, J. R.:* Surg. Gynec. Obst. **16:** 315, 1913. (11) *Proper, M. S., and Simpson, B. T.:* Surg. Gynec. Obst. **29:** 39, 1919. (12) *Regaud, C., and Lacassagne, A.:* Strahlentherapie **37:** 275, 1930. (13) *Seitz, L., and Wintz, H.:* Unsere Methode der Röntgen-Tiefentherapie und ihre Erfolge, Berlin, 1920, Urban und Schwarzenberg, p. 355. (14) *Steinhardt, B.:* Wien. klin. Wchnschr. **37:** 844, 1924. (15) *Unbehaun, G.:* Klin. Wchnschr. **11:** 1152, 1932. (16) *Veit, J.:* Handbuch d. Gynäkologie, ed. 2, Vol. 3, p. 516, 1908. (17) *Vogt, M. E.:* Am. J. Obst. & Gynec. **5:** 523, 1923.

HERNIAS INTO THE BROAD LIGAMENT AND REMARKS ON OTHER INTRAABDOMINAL HERNIAS

JAMES C. MASSON, M.D., AND WALTER ATKINSON, M.D., ROCHESTER, MINN.
(From the Mayo Foundation and the Division of Surgery, the Mayo Clinic)

HERNIA into the broad ligament, or between the folds of it, is difficult to explain. We have not been able to find any embryologic or traumatic factor that would predispose to development of such hernias. There are normally shallow fossae between the round ligaments and the fallopian tubes, and again between the fallopian tubes and the uteroovarian ligaments, which might possibly be deepened. It is conceivable, also, that the peritoneum might be torn in these situations, as the result of increased intraabdominal pressure, or of trauma during labor. This has been suggested by some authors as a predisposing cause of hernia in the situations named. We are unable to find any explanation for the formation of a pouch or hernial sac between the folds of the broad ligament below the uteroovarian ligament. It is interesting and probably significant to note, however, that at this point the broad ligament is very thin, there is practically no supporting tissue between the two folds of peritoneum, and consequently there is a very poor blood supply.

REPORT OF CASE

The patient whose case we are reporting in detail and whose condition prompted us to take up this topic came to the Mayo Clinic in 1924. She was then twenty-six years old. Both her parents had syphilis; otherwise the family history was negative. Besides the ordinary diseases of childhood she gave a history of frequent sore throat, malaria, and dengue fevers. When she was eighteen years of age, a stem pessary had been inserted into her cervix. Shortly before she came to the clinic she had received an electric shock from a roentgen ray machine in a dentist's office. She had not suffered other accidents.

At the time of her admission, the conditions of which she complained were mostly functional, but she had infected tonsils and syphilis. Under appropriate treatment the Wassermann reaction of the blood has remained constantly negative.

She returned to the clinic Feb. 6, 1933, and reported that she had married in the interim. She complained of pain in the right lower abdominal quadrant during the menstrual period; this had first appeared after the birth of her only child, two and one-half years before. Menstrual flow was profuse and, as a rule, periods of flow came more frequently than formerly. However, in December there had been no flow, and in January the discharged blood had been abnormally dark. Since onset of the menstrual irregularities pain in the right lower abdominal quadrant had been constant, more severe, and associated at times with nausea. Vaginal discharge had been of sufficient amount to necessitate the wearing of a napkin. For two months before the patient came to the clinic she had frequency of urination and some pain in the region of the bladder. She was constipated and straining at stool accentuated

the pain in the right lower abdominal quadrant. Her physician, at her home, had diagnosed a tumor the size of an orange in her right ovary, and had advised operation. One breast, also, had been sore recently.

Examination of urine and blood gave negative results. Colostrum was expressed from the right breast. The abdomen was negative to examination. The uterine cervix was patulous and soft, but the body of the uterus was firm and not enlarged. A tender mass, measuring about 5 by 5 cm., was palpable in the right adnexal region, and ectopic pregnancy was seriously considered in spite of a negative Friedman test.

Feb. 9, 1933, the pelvis was explored. At this time, dilatation and curettage disclosed evidence of hypertrophic endometritis. Through an incision low in the median line pelvic exploration was made, and revealed the right ovary and part of the right tube firmly held in, but not adherent to, a hernial sac which opened on the posterior surface of the right broad ligament, just below the uteroovarian ligament (Fig. 1). The left fallopian tube apparently was normal and the left ovary, cystic.

There is no doubt that the internal hernia was the cause of the patient's symptoms. An attempt was first made to save the right ovary, but it was traumatized so extensively that it was thought advisable to remove it along with the tube. The left ovary was resected on account of multiple, small cysts, leaving tissue equal to about a third of an ovary of normal size. The appendix gave evidence of having

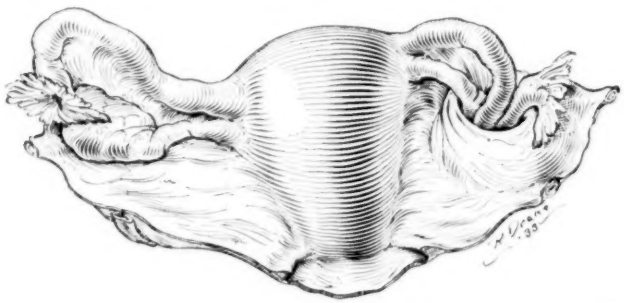


Fig. 1.—Herniation of right ovary and part of right tube into the sac between folds of the right broad ligament.

undergone pathologic change in the past and was removed. There were no stones in the gallbladder. The hernial sac was obliterated as much as possible by a running purse string suture of chromic catgut. The patient made an uneventful recovery, and in a letter dated Mar. 21, 1934, she wrote that she had been very well since the operation, but that she was seven months pregnant and had some pain in the right side.

In all previously reported cases the patients were operated on for acute intestinal obstruction, or the hernia was found at postmortem examination.

REVIEW OF LITERATURE

Only a very few cases have been reported in which the hernia has extended into or through the broad ligament. The condition seems to be rare. Moynihan's monograph on internal hernia, published in 1906, contains no reference to hernia into the broad ligaments of the uterus. The same is true of the collection of reports made by Short in 1915. However, in 1925, Short again wrote on internal hernia and collected all reports of cases published since 1915. He referred to four cases in which hernia had been reported to be into, or through, the broad ligaments. In addition to the cases collected by Short, we were able to find reports of eight cases. In two of these,

hernia occurred between the folds of the broad ligament; in five, a loop of small bowel was strangulated by passing completely through the broad ligament, and in one we were unable to obtain exact information as to what had happened, except that the broad ligament was invaded by the hernia. After this paper had been prepared, an article on nearly the same subject appeared under the authorship of Hunt. We then revised our paper. Hunt referred to all the cases we had listed, also to one of Dunn, to another of Stimson, and to one new case from the University of Chicago Clinic. He also recorded two cases in which openings were found in the broad ligaments without herniation of any viscus. In one of these two cases, reported by Hermann, defects were found on the posterior surface of each broad ligament, and in the other, reported from the Chicago University Clinic, two fenestrae were present in the right broad ligament. Hunt appended to his paper a supplementary report of a case, also seen in the University of Chicago Clinic, in which intestinal obstruction, but no hernia, followed a Baldy-Webster operation. The four reports cited by Short, the eight found by us, and the three which we included after we had read Hunt's article are noted in Table I.

TABLE I. REPORTED CASES OF HERNIA BETWEEN LAYERS OF, OR THROUGH, THE BROAD LIGAMENT*

AUTHOR	CASE	DATE	TYPE OF HERNIA	SIDE
Quain	1	1861	Exact type not known	Right
Fagge	2	1917-18	Between layers	Right
			Between layers	Left
Barr	1	1920	Not known	
Richardson	1	1920	Through	Right
Pidcock	1	1924	Through	Left
Dunn	1	1926	Through	Left
Dornan	1	1928	Between layers	Left
Stimson	1	1928	Through	Right
Janes	2	1929	Between layers	Left
			Through	Left
Pemberton and Sager	1	1929	Through	Left
Caplan	1	1930	Through	Right
Cooper	1	1931	Through	Right
Hunt	1	1934	Between layers	Left

*Intestine involved in all cases.

In Quain's case, the bowel was constricted at two different points. At one point there was a loop formed by old adhesions between the right broad ligament of the uterus and the mesentery. At the other point there was a simple fissure in the peritoneal fold, forming the false ligament on the same side. The bowel passed through the latter opening and then through the former. In explanation, Quain stated that the unusual position of the uterus, which was obliquely placed, with the right cornu held firmly toward the spine, may have been assumed in one of the patient's pregnancies when inflammation of the right broad ligament took place and it became adherent to the mesentery. The peritoneal reflection of the broad ligament was put on stretch and became fissured. This condition was found at postmortem examination.

In Fagge's first case, there was an opening in the left broad ligament just below, and medial to, the ovarian ligament. The bowel passed from behind forward, into a pouch in the broad ligament, and filled Douglas' pouch. The opening was closed with a continuous catgut suture. The patient recovered following operation. In his second case, the pouch was above the ovary and its ligament. The intestine passed into it from behind. Recovery following operation was uninterrupted.

Short listed a case reported by Barr, but we were not able to get Barr's original article, and we do not know the exact situation or type of the hernia, but apparently it was situated just below the round ligament, probably in the fossa between the round ligament and the fallopian tube. The patient recovered following operation, in which it was necessary to resect 8 feet (about 250 cm.) of bowel.

In Richardson's case the hernia followed a Baldy-Webster operation performed two years previously. At exploration, Richardson found the point of obstruction to be in the region of the right broad ligament. The perforation was external to the right round ligament which passed through the opening. Perforation was not found in the left broad ligament. The patient made a good recovery following the operation.

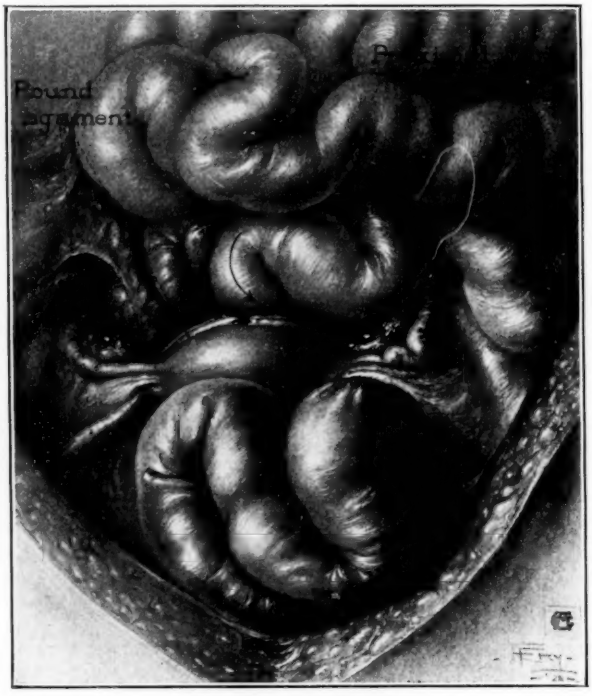


Fig. 2.—Strangulated loop passing through the broad ligament.

In Pidcock's case, the hernia occurred fourteen days after normal delivery. The strangulating agent was the left round ligament, and the fenestra lay below it. The ligament measured 4 inches (10 cm.); the middle 2 inches (5 cm.) were free from the broad ligament. Thus, the subjacent coils of intestine were bridged over and strangulated. It was necessary to resect a portion of the bowel, following which the patient made a good recovery. Pidcock stated further that, after investigating ten bodies of women, all probably parous, he found that he was able to stretch the round ligament forward, and to demonstrate a thin, apparently avascular fold of peritoneum joining it to the main part of the broad ligament. On no occasion was great force required to perforate this "mesoligamentum teres" with his finger. He suggested that possibly, after pregnancy, all the structures connected with the uterus were relaxed, and that in some manner a coil of intestine had ruptured this mesoligamentous fold.

Dornan's patient was a multipara whose only previous operation was one for repair of a strangulated femoral hernia nine years before. The point of strangulation was at the neck of a peritoneal invagination into the posterior aspect of the left broad ligament. Dornan incised the neck of the sac and then obliterated it by sutures. The patient recovered following the operation.

In Janes's first case the opening was in the left broad ligament. The bowel entered the opening from in front and lay for the most part in the pouch of Douglas. The opening was a little less than 2 cm. in diameter and lay below the round ligament and fallopian tube, immediately lateral to the uterine vessels. No sac was present. The patient made an uneventful recovery. In his second case an opening 1.5 cm. in diameter was found in the left broad ligament. The opening had a double margin and gave the appearance of a double ring. There was no pouch. As represented in drawings, the opening appeared to be in the ligamentous fold, between the round ligament and the fallopian tube, the bowel entering from in front. The

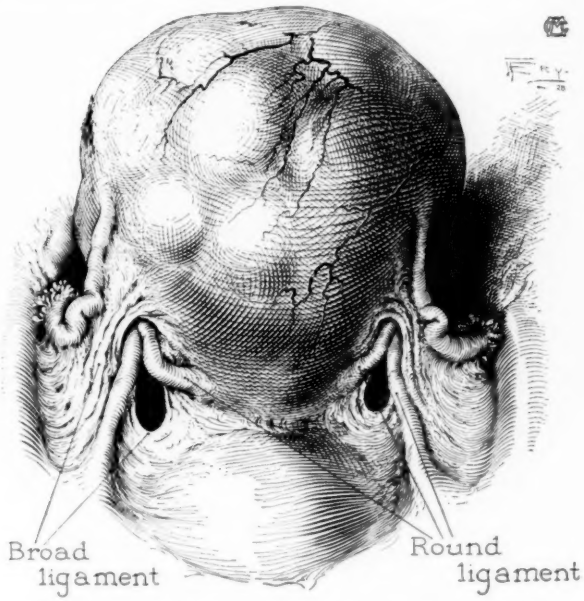


Fig. 3.—Baldy-Webster operation, complicated by a fibromyomatous uterus; large openings may be noted in both broad ligaments.

patient died from cardiac failure seventeen hours after operation. In a recent communication, Janes stated that neither of his patients had been operated on before.

Pemberton and Sager reported a case in which obstruction followed a Baldy-Webster operation performed ten days before (Fig. 2). Strangulation occurred through the aperture made in the left broad ligament in the course of the Baldy-Webster operation. The intestine had herniated from the posterior aspect. It was necessary to resect a portion of the bowel in this case, but the patient recovered. Pemberton and Sager also reported a case, not of hernia, in which a Baldy-Webster operation had been performed twelve years before. They operated for multiple fibroids of the uterus and found, incidentally, a large opening in each broad ligament, either of which would admit two fingers, at the site of the old Baldy-Webster operation (Fig. 3). There was no evidence of obstruction, but the openings were potential sites of obstruction.

Caplan stated that the opening in his case was through the right broad ligament, between the ovary and the uterus, about ½ inch (1.2 cm.) below the fallopian tube. Obstruction was relieved and the patient made an uneventful recovery.

In Cooper's case abdominal operations had not been performed previously. The opening was in the right broad ligament; the intestine entered from the posterior aspect. The edges of the opening were thin, suggesting recent formation. The right tube was compressed and almost gangrenous from the tension imposed on it. Judging from the drawings accompanying Cooper's paper, the intestine passed between the tube and the right round ligament. The patient made an uneventful recovery.

In Dunn's case, a woman, aged forty-four years, fell off a chair in 1904 and had a miscarriage three days later. For more than a year thereafter she had severe abdominal pain on lifting or holding her child. The pain persisted for fifteen years when she was lying on her side, except when she was pregnant. Reaching upward caused severe pain. The patient had four labors and two miscarriages after the time of the accident. Intercourse had been painful in the past four years. At operation, 15 inches (37.5 cm.) of bowel were found protruding through an opening in the left mesosalpinx, and on examination a similar opening was noted on the right side, without a hernia. The opening was closed and the left tube removed. Convalescence was uneventful except for an accumulation of serous exudate which necessitated colpotomy.

In Stimson's case, a woman, aged thirty years, was admitted to the hospital in an almost moribund condition. She had a history of having had intestinal obstruction for four days, with marked tenderness above the right Poupart's ligament. At operation the greater part of the small intestine was found to be gangrenous as the result of strangulation through an opening in the right broad ligament. The patient died.

Hunt's patient, aged twenty-five years, had had two previous cesarean sections for dystocia. During the course of low, cervical cesarean section, a considerable portion of large bowel and some omentum were found in the anterior part of the left pelvis. On investigation, an opening was found in the posterior surface of the left broad ligament, below the ligamentum proprium ovarii. The hernial sac was between the layers of the broad ligament. The incision through the vesical peritoneum had exposed the herniated bowel and omentum. There was no indication of constriction or adhesions, and gentle traction easily reduced the hernia. The opening measured 4 by 5 cm. and was elliptical. It was closed by suture. Convalescence was entirely normal.

It will be noted that in at least two of the cases reported in the literature intestinal obstruction resulted from a loop of bowel becoming caught in an opening made in the broad ligament during the course of a Baldy-Webster operation for retroversion. This should impress us with the necessity of accurately fixing the edges of the opening in the broad ligament to the round ligaments, as advised by both Webster and Baldy.

SUMMARY AND CONCLUSIONS

Broad ligament hernias may be either into a pouch between the layers of the broad ligament, or in an opening through both layers of the broad ligament. The ileum is the viscus that most frequently becomes herniated. The ovary may become incarcerated in the hernial

opening as it did in our case. There has been no satisfactory embryologic explanation of the formation of a retroperitoneal fossa in the broad ligament, or of a fissure through the broad ligaments. Rupture of the peritoneum covering the broad ligament during gestation or at the time of delivery probably accounts for most cases. Perforation of the broad ligaments, such as is made in the course of the Baldy-Webster operation, predisposes to hernia of the type we are considering.

OTHER INTRAABDOMINAL HERNIAS

The foregoing material is, as far as we know, a complete consideration of hernias into the broad ligament, and we have treated this material as a unit, reporting what we have found in the literature; reporting our case, and drawing our conclusions. That part of our paper we hope will stand as a compilation to which others can safely refer in the future.

However, hernias into the broad ligament are only one variety of intraabdominal hernia, and intraabdominal hernia frequently is associated with intestinal obstruction. These conditions are of vital interest to the practicing surgeon.

We have mentioned the need of closing tears in the broad ligament after the Baldy-Webster operation. We would like to devote a few more words to practical aspects of our subject.

Symptoms of acute or chronic intestinal obstruction affecting a female are just as much problems for gynecologists as for general surgeons. The cause of the obstruction may be some pathologic condition primary in the genital organs or a condition secondary to some inflammatory or operative procedure in the pelvis. As soon as possible after diagnosis is made, the abdomen should be explored, the obstruction relieved, the necessary procedures taken to prevent recurrence of the obstruction, and, in case of gangrene, resection and anastomosis of the bowel and perhaps proximal enterostomy performed.

Intraabdominal hernias may be primary when they occur as the result of some congenital anomaly, or secondary to some inflammatory or postoperative condition. In the past, a diagnosis was rarely made during life unless intestinal obstruction sufficient to warrant abdominal exploration resulted. At present roentgenograms are made in most abdominal conditions in which there are indefinite or mixed symptoms, and occasionally a correct diagnosis of internal hernia is made, but the majority of such hernias are still found accidentally in the course of an operation for some other condition, or at postmortem examination.

Under these conditions, time spent in differential diagnosis is time ill spent. The decision to be made is whether or not the condition is surgical. The chagrin of the surgeon who operates and fails to find a surgical condition is nothing to that of the surgeon who does not operate in time.

REFERENCES

(1) *Caplan, S.:* Brit. M. J. **1:** 950, 1930. (2) *Cooper, R. W.:* Australian & New Zealand J. Surg. **1:** 325, 1931. (3) *Dornan, W. E.:* Brit. M. J. **2:** 528, 1928. (4) *Fagge, C. H.:* Brit. J. Surg. **5:** 694, 1918. (5) *Hunt, A. B.:* Surg. Gynec. & Obst. **58:** 906, 1934. (6) *Janes, Robert:* Brit. J. Surg. **17:** 333, 1929. (7) *Moynihan, B. G. A.:* Retroperitoneal Hernia, ed. 2, London, 1906, Bailliere, Tindall and Cox. (8) *Pemberton, J. deJ., and Sager, W. W.:* S. Clin. North America **9:** 203, 1929. (9) *Pidcock, B. H.:* Brit. M. J. **1:** 369, 1924. (10) *Quain, Richard:* Tr. Path. Soc. London **12:** 103, 1860. (11) *Richardson, E. P.:* Surg. Gynec. & Obst. **31:** 90, 1920. (12) *Short, A. R.:* Brit. J. Surg. **12:** 456, 1925.

THE HAULTAIN OPERATION FOR INVERSION OF THE UTERUS

KARL M. WILSON, M.D., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry)

NO FEWER than twelve different operative procedures have been suggested for the correction of inversion of the uterus after the acute phase has passed or the condition has become chronic and manual reduction has become impossible. Most of these operative procedures are carried out by the vaginal approach and range from the simple incision of the posterior portion of the constricting cervical ring as suggested by Hirst, to the more extensive colpohysterotomies of Küstner and Spinelli. The latter, the procedure which is most widely employed, is the one which is usually advised in practically all of the American and British textbooks.

T. Gaillard Thomas was the first to suggest abdominal operation for this condition. In 1869 he successfully reduced an inversion of long standing by dilating the constricting cervical ring with a metal dilator, through a small abdominal incision. The procedure proved to be difficult and consumed a considerable period of time.

The procedure which I wish to discuss was first described by Haultain in 1901. The operation is a very simple one and, according to Haultain's original technic, consists simply in a low midline abdominal incision to expose the constricting cervical ring from above. After proper exposure, the ring is incised in the midline posteriorly, and the resistance being thus overcome, the inversion is corrected by pressure from below, an assistant with two fingers in the vagina making gentle pressure against the inverted fundus. After the uterus is returned to normal position, the uterine wound is sutured in two layers, and the abdominal wound is closed. It is interesting to note that two years previously, Everke suggested a somewhat similar procedure. After laparotomy he incised the constricting ring anteriorly.

Having done this, he still found it impossible to replace the uterus and was obliged to make a second incision posteriorly.

Haultain's first patient presented an inversion of nine months' standing. In 1907 he presented three other cases treated successfully in a similar manner, but with a slight modification in the technic. This consisted in introducing a finger through the uterine incision to a point below the inverted fundus and effecting reduction by making

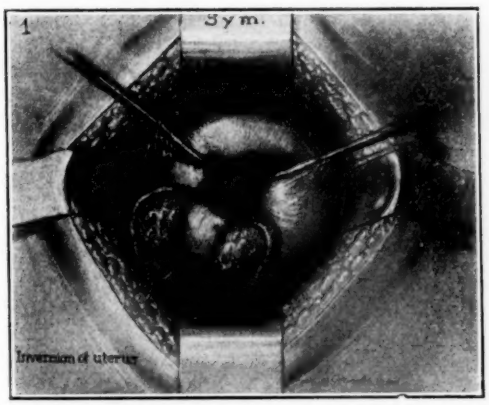


Fig. 1.—The appearance of the inverted uterus as it appears when viewed from above. In this instance the tubes and ovaries did not descend into the pit of the inversion.

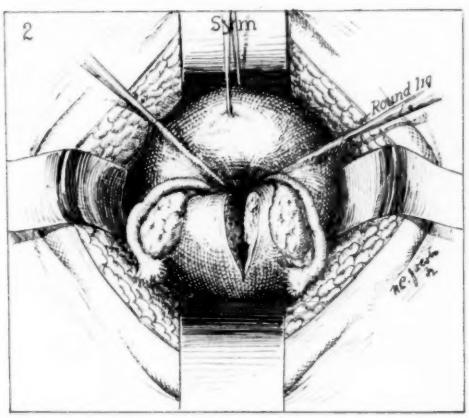


Fig. 2.—The site and usual extent of the incision made in the middle of the posterior portion of the constricting ring are shown. The uterus can now be replaced by pressure from below, through the vagina. If it should prove necessary, the uterine incision may be enlarged somewhat.

pressure with this finger against the fundus. Two of these patients subsequently became pregnant, one giving birth to one and the other to two full-term children; the pregnancies and labors were uneventful in each case.

Munro Kerr has made use of Haultain's procedure with success. He mentioned one instance in which the uterus had become so friable as

a result of a long standing inversion as to necessitate its removal after its replacement. One of the first, if not the first, operation of this type to be done in this country, was performed by the late J. Whitridge Williams in 1905. I am indebted to Dr. J. M. Bergland for the privilege of presenting the history which briefly is as follows:

CASE 1.—J. H. H., a twenty-one-year-old primipara, was delivered in her home by low forceps followed by spontaneous extrusion of the placenta. A severe postpartum hemorrhage occurred; the attending physician estimated the blood loss at 2,000 c.c. The bleeding was controlled by massage, but the patient showed signs of collapse, responding, however, to stimulation. Three days later she complained of difficulty on urination, and examination at this time revealed a complete inversion of the uterus. She was seen by Dr. Williams at this time and was sent to the hospital.

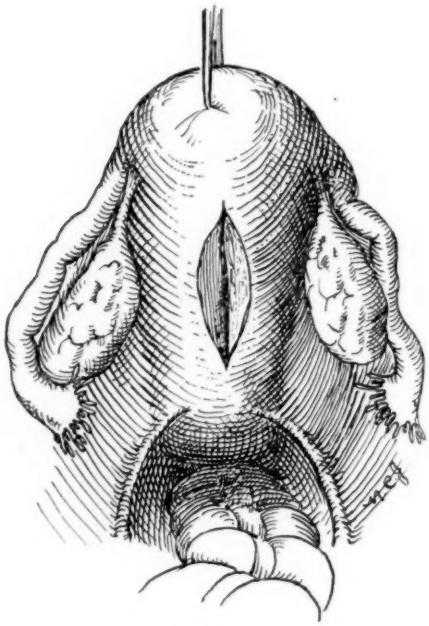


Fig. 3.

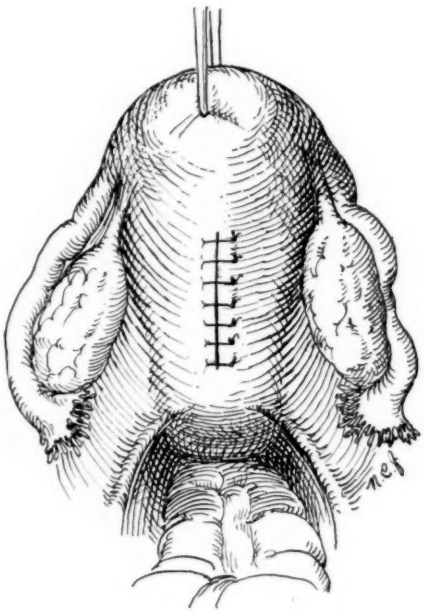


Fig. 4.

Fig. 3.—Diagrammatic illustration of the uterus after replacement. The uterine incision will be closed in two layers.

Fig. 4.—The uterine incision is closed. If malposition of the uterus is noted, some form of suspension may be employed.

By catheterization, 1,400 c.c. of urine were withdrawn. Temperature was 100° F.; pulse, 132. Operation according to the Haultain technic was carried out the next day, four days postpartum. An incision about 4 cm. in length was made through the posterior portion of the cervical ring and attempts were made to reduce the inversion by inserting the fingers through this. These efforts did not succeed, and it became necessary to extend the incision toward the fundus for a distance of about 10 cm. before the inversion could be corrected. There was little bleeding. The postoperative course was rather stormy for the first ten days, with a rapid pulse and marked febrile reaction, the highest temperature being 103.6° F. on the sixth day. Convalescence was also complicated by a wound infection. She was discharged on the twenty-first day in good condition. Her subsequent history is unknown.

CASE 2.—A nineteen-year-old woman, delivered of her first baby by forceps seventeen days previous. A postpartum hemorrhage occurred at the time, and irregular bleeding continued thereafter. She was admitted to Strong Memorial Hospital because of weakness and the persistent bleeding. She was markedly anemic; hemoglobin, 25 per cent; R.B.C. 1,200,000; W.B.C., 17,200; temperature, 38.4° C.; pulse, 140. Pelvic examination revealed a complete inversion of the uterus, which, however, was well involuted for the period. Examination caused considerable bleeding. She continued to show evidence of infection for several weeks after admission, with an irregular temperature curve and increased leucocyte count. She also had repeated vaginal hemorrhages, which at times were of considerable amount. These were controlled by mercurochrome gauze packs. There was some superficial sloughing in the region of the inverted fundus, causing a vaginal discharge with offensive odor. To combat the effects of repeated blood loss, she was given numerous transfusions, eleven in all. Eight weeks after admission, her condition had improved sufficiently to warrant operation; hemoglobin, 59 per cent; normal temperature, and leucocyte count for a week; and although there was still a slight vaginal bleeding, the uterus appeared clean, and it had involuted to approximately normal size. On June 28, 1930, under anesthesia, an attempt to reduce the inversion manually was unsuccessful. The abdomen was then opened, and the typical Haultain technic was followed, the uterus being replaced by pressure from below by an assistant after a small incision had been made in the middle of the cervical ring posteriorly. After the uterus was replaced, the incision was found to be slightly less than an inch in length. It was closed in two layers, (1) an intramuscular layer of several interrupted catgut sutures and (2) a continuous seromuscular layer. It was then found that the uterus tended to lie in retroversion, so uterine suspension was carried out, the Simpson technic being followed. Her convalescence was entirely satisfactory, a temperature of 38° C. on the fourth postoperative day being the only elevation noted. She menstruated normally within a month after operation and continued to do so for a year, when she then became pregnant again. She was followed in my service, the pregnancy, labor, and puerperium being entirely uneventful. A second spontaneous labor occurred in April, 1934.

CASE 3.—A twenty-nine-year-old para i, seen in consultation with Dr. Shirley R. Snow, Jr., was delivered by low forceps after a thirty-six-hour labor, placenta expressed by the Credé method after twenty-five minutes, no force necessary. The third stage was attended by only moderate bleeding, but the patient went into shock, and at this time a small dimpled depression was noted at the fundus. After transfusion she recovered from the shock. The puerperium was uneventful, with no excessive bleeding, and she was discharged on the fourteenth day. The uterus appeared to involute well and was palpable just above the symphysis at the time of discharge. Lochia continued scant, and she was up and about her house. Three weeks after discharge she had a fall, this being followed by a rather brisk hemorrhage. She was not seen at this time, but three days later, as the bleeding continued, she called Dr. Snow, who on examination discovered a complete inversion of the uterus.

On admission to the hospital she showed a considerable degree of anemia, hemoglobin, 55 per cent; R.B.C. 3,500,000; W.B.C. 5,600. The temperature was 36.5° C.; pulse, 80. Except for the anemia, her general condition was good, and there was no evidence of infection. She was given a transfusion of 500 c.c., and operation according to the Haultain technic was carried out two days after admission—five weeks postpartum. The length of the uterine incision necessary to effect reduction was 1 inch. Following the closing of the uterine incision, the uterus, which had involuted to practically normal size, lay in good position; suspension was not necessary. Except

for a rise in temperature to 38.6° C. on the day after operation, her convalescence was entirely uneventful. Normal menstruation was reestablished within a month. No pregnancies have occurred since.

DISCUSSION

The advantages of this procedure as compared with the more frequently performed Spinelli operation are several. It is extremely simple and can be done in fifteen to twenty minutes. Hemorrhage is minimal but is easily controlled if it should occur. Any displacement of the uterus noted after its completion can be corrected at the time. Most important is the minimal trauma done to the uterus, a very small uterine incision being all that is usually needed to effect replacement. This is of particular importance from the standpoint of future childbearing, and it is obvious that the longer the uterine incision and the greater the scar tissue formation, the greater would be the possibility of rupture occurring in future pregnancies. In carrying out this procedure, I would emphasize the advisability of incising the constricting ring as it lies, rather than attempting to push or draw the uterus up as far as possible before making the incision. If the latter maneuver be attempted, the incision and subsequent scar will be high up in the uterine wall, and will be subjected to greater strain in the event of subsequent pregnancies. I consider this operation to be distinctly contraindicated in the presence of active infection.

It is true that most of the previously reported series of inversion treated by abdominal operation have shown a high mortality, from 16 to 21 per cent. Some of these series, however, included operations performed a good many years ago before the days of improved surgical technic, and others include acute cases where the mortality is bound to be high if operation is carried out while the patient is still in a state of shock. Irving very properly lays particular stress on this point, and he and Huntington have had a very satisfactory experience with abdominal operation, though Huntington's procedure does not involve any uterine incision.

The Haultain operation, if undertaken early in the puerperium before involution is complete, is bound to be difficult and will require a long uterine incision before the enlarged fundus can be replaced. This will predispose to infection and may well leave an uterus which will be unsuited for future childbearing. This difficulty is well illustrated in Case 1. The operation will be greatly facilitated if not done until the uterus has approached its normal size by involution.

This small group of cases obviously does not permit one to draw any sweeping conclusions. They are presented rather in the hope of reviving interest in a procedure which has received little attention in this country and which has impressed me as an excellent one in properly selected cases

SUMMARY AND CONCLUSIONS

Three examples of inversion of the uterus treated by the Haultain operation are presented—with no mortality.

The chief advantages lie in its simplicity and minimal trauma to the uterus.

The optimum time for its performance is after involution is complete or nearly so.

It is contraindicated in the presence of active infection.

REFERENCES

Everke: Monatschr. f. Geburtsh. u. Gynäk. **9:** 89, 1899. *Haultain, F. W. N.:* Brit. M. J. **2:** 974, 1901; Proc. Roy. Soc. Med. (Obst. Sec.) **1:** 279, 1907-08. *Hirst, B. C.:* Am J. Obst. **41:** 1900. *Irving, F. C.:* Obstetrics and Gynecology, Curtis, 1934. *Kerr, Munro:* Clinical and Operative Gynaecology, New York, 1922, Oxford University Press. *McCullogh, W. McK.:* J. Obst. & Gynaec. Brit. Emp. **32:** 280, 1925. *Thomas, T. Gaillard:* Am. J. Obst. **2:** 423, 1869.

SYPHILIS OF THE PLACENTA

The Histologic Examination of 1,085 Placentas of Mothers With Strongly Positive Blood Wassermann Reactions

James R. McCord, M.D., Atlanta, Ga.

(From the Department of Obstetrics and Gynecology, Emory University School of Medicine)

IN 1929 I presented before this Society "A Study of Two Hundred Fetal Autopsies."[1] I made the following statement: "The histologic diagnosis of syphilis in a placenta at or near term is, as a rule, an easy diagnosis to make. I agree with Holland that the histologic diagnosis of syphilis in a premature placenta is exceedingly difficult. The more premature the placenta, the more difficult it is to express an opinion." The same year in a publication, "Syphilis and Pregnancy,"[2] I made this statement: "The statement has been made that there is no distinctive histologic picture of syphilis of the placenta. Literally, that statement is probably true; interpreted in a broad, practical way, it is not true. . . . The microscopic field of a mature or near-mature syphilitic placenta with its large, crowded villi, the increase of connective tissue and the almost complete loss of vascularity, occurs often enough to be of distinct diagnostic aid."

Increasing experience has caused me to form gradually the opinion that the histologic diagnosis of syphilis of the placenta is laden with many difficulties and to question its practical value as a routine method of determining congenital syphilitic infection. This study is an effort to evaluate the histologic diagnosis of syphilis of the placenta at all

stages of pregnancy, of stillborn babies as well as of babies born alive. It seems to show that the more premature the placenta, the more difficult it is to make a diagnosis of syphilis.

The diagnosis of syphilis of the placenta was attempted only along well-established lines: the enlargement and crowding of the villi, the presence of connective tissue in varying degrees of density,* an increase of the stroma cells,† and a lessening of or an absence of the vascular supply of the villi.

The study is based on the microscopic examination of 1,085 placentas, all of women with strongly positive blood Wassermann reactions. The 1,085 pregnancies were classified as follows: at or about term, 742; premature, 220; and abortions, 123.

Mature Placentas (742).—Babies weighing 2,500 gm. or more at birth and pregnancies reported as at or about term, without the birth weights, were studied as term issues. Seven hundred and forty-two women went to term; 679 of these gave birth to live babies. Sixty-three babies were stillborn or died in the nursery during the first few days of life.

Term Babies Born Alive (679).—One hundred and seventy-four of the 679 mothers who had live babies, at or about term, received no prenatal antisyphilitic treatment; 276 received fewer than 7 treatments; and 229 received 7 or more treatments.‡

The diagnoses of the placentas of the 174 mothers who received no treatment were negative in 163; probably negative, 4; premature and probably negative, 2; premature and negative, 2; and probably positive, 3. It should be remembered that these 174 mothers had strongly positive blood Wassermann reactions; none of them received any prenatal antisyphilitic treatment; all left the hospital with living babies; and not a placenta was thought to be syphilitic and only 3 probably so. The placentas of the 276 mothers who received fewer than 7 treatments were negative in 264; probably negative, 2; premature, 1; premature and probably negative, 1; positive, 3; and probably positive, 5. The placentas of the 229 mothers who received 7 or more treatments were diagnosed negative in 224 and probably negative in 5.

It is significant that of 679 placentas of live term babies, all of strongly positive Wassermann mothers, only 3 were syphilitic and 8 probably so.

Term Babies Stillborn or Died in the Hospital (63).—The mothers of 45 of these babies received no treatment; 7 received fewer than 7 treatments, and 11 received 7 or more treatments.

The placentas of the 45 mothers who received no treatment were negative in 25; probably negative, 1; premature, 4; premature and probably negative, 1; premature and probably positive, 3; positive, 2; probably positive, 8; and premature and negative, 1. Six of the placentas of the 7 mothers who received less than 7 treatments were negative and one was positive. All of the placentas of the 11 women who received 7 or more treatments were negative.

There were as many syphilitic or probably syphilitic placentas (11) found from 63 stillborn babies at term as were found from 679 live babies at term.

---

*Chronic nephritis eliminated.

†An increase of stroma cells proper; histiocytes or Hofbauer cells, without other evidences, were not considered diagnostic of syphilis.

‡A treatment consists of the intravenous administration of 0.45 gm. neosalvarsan and a mercurial inunction. This is given weekly. (For the past two years, an additional inunction has been given to all patients—two weekly.)

Autopsies on Term Babies (33).—Autopsies were performed on thirty-three of the 63 stillborn term babies. The mothers of 24 of these babies received no treatment. In 13 of the 24 babies, the organisms of syphilis were found in the stained tissues and the long bones showed, by roentgen ray examination, the characteristic, moth-eaten lesions that are believed to be pathognomonic of fetal syphilis. The results of the placental examinations of the 13 babies were negative in 1; premature, 4; premature and probably positive, 2; positive, 1; and probably positive, 5. In 2 babies, the organisms of syphilis were found, but changes in the long bones could not be demonstrated. Both of the placentas were negative for syphilis. In 9 babies, the organisms of syphilis were not found, and changes in the long bones could not be seen. Eight of the placentas were negative, and one was premature and negative.

The organisms of syphilis could not be found, and there were no long-bone changes seen in the 3 stillborn term babies whose mothers had fewer than 7 treatments. The 3 placentas were negative for syphilis.

The mothers of 6 stillborn term babies received 7 or more treatments. In 5 babies, the organisms of syphilis were not found; there were no long-bone changes, and all the placentas were negative. In one baby, the organisms were not present; a roentgenogram was not made; and the placenta was negative.

Placental Histology of Live Term Babies Checked With the Long-Bone Changes (101).—Roentgen ray examinations of the long bones were made of 101 live term babies and the placental histology was checked with the long-bone changes.

The mothers of 19 of these babies received no treatment. Long-bone changes were present in 5 babies, and the placentas were negative. The long bones were negative in 14; 13 of the placentas were negative, and one was probably negative.

Forty-four mothers received fewer than 7 treatments. No long-bone changes, suggestive of syphilis, were found in any of the babies. Forty-three of the placentas were negative, and one was premature and probably negative.

The mothers of 38 of these live babies received 7 or more treatments. The long bones showed evidence of syphilis in one baby; the placenta was negative. In the remaining 37 babies, long-bone changes were not seen; 36 of the placentas were negative, and one was probably negative.

Placental Histology of Stillborn Term Babies Checked With the Long-Bone Changes (54).—Sixty-three babies were stillborn, at or about term, or died in the hospital. Roentgen ray examinations and placental studies were made of 54.

No prenatal antisyphilitic treatment was given to 39 of the 54 mothers. Long-bone changes indicative of syphilis were found in 20 of the babies. The placentas were negative in 5; premature, 4; positive, 2; premature and probably positive, 3; probably positive, 6. There were no long-bone changes found in 19. The placentas were negative in 16, probably negative, 1; probably positive, 1; and premature and negative, 1.

Six mothers received fewer than 7 treatments. The long-bone changes of syphilis were seen in 2 babies; one of the placentas was negative; the other, positive. The long bones were normal in 4 babies, and the 4 placentas were negative. Nine mothers received 7 or more treatments. No long-bone changes were found in any of the babies. All the placentas were negative.

Premature Placentas (220).—Babies weighing from 1,500 to 2,500 gm. at birth and pregnancies reported as from seven to eight months' gestation, without the birth weights, were classified as premature. Two hundred twenty placentas of premature issues were studied. Seventy-eight of the babies were born alive; 142 were stillborn or died in the hospital during the first few days of life.

Premature Born Alive (78).—The mothers of 21 of these babies received no prenatal antisyphilitic treatment; 38 received fewer than 7 treatments; and 19 received 7 or more treatments.

The placentas of the 21 mothers who received no treatment were negative in 12, premature and probably negative, 2; premature, 1; premature and probably positive, 2; positive, 1; probably positive, 1; and premature and negative, 2.

The placentas of the 38 mothers who received fewer than 7 treatments were: negative in 27; premature and probably negative, 2; premature, 4; premature and probably positive, 1; positive, 2; and premature and negative, 2.

The placentas of the 19 mothers who received 7 or more treatments were negative in 16; premature, 1; premature and probably positive, 1; and premature and negative 1.

Premature Stillborn or Died in the Hospital (142).—No treatment was given to the mothers of 100 of these babies. The placentas were negative in 24, probably negative, 1; premature, 15; premature and probably negative, 10; premature and probably positive, 22; positive, 16; probably positive, 4; premature and negative, 4; and premature and positive, 4.

The mothers of 35 of these babies received fewer than 7 treatments. Twelve of the placentas were negative; 7 were premature; 3 were premature and probably negative; 3 were premature and probably positive; 2 were positive; 2 were premature and positive; and 6 were premature and negative.

There were only 7 mothers in this group who received 7 or more treatments. Six of the placentas were negative, and one was premature and negative.

Autopsies on Premature Babies (54).—Autopsies were performed on only 54 of the 142 stillborn premature babies. The mothers of 46 of these babies received no treatment. The organisms were found, and there were changes in the long bones in 32 babies. The placental findings were negative in 8; premature, 4; premature and probably negative, 1; premature and probably positive, 9; premature and negative, 1; premature and positive, 4; and positive, 5. The organisms of syphilis were found in 4 babies in whom there were no long-bone changes. The placentas were premature and probably negative in 1; premature and probably positive, 1; premature and negative, 1; and positive, 1. No organisms were found nor any long-bone changes seen in 7 babies. Three of the placentas were negative; 3 were premature; and 1 was premature and negative. There were long-bone changes in 3 babies in whom the organisms could not be found. One of the placentas was negative; the other 2 were positive.

The mothers of 6 babies received fewer than 7 treatments. The organisms of syphilis were found in 2 babies, but no changes were seen in the long bones. One placenta was premature, and the other was premature and negative. There were no organisms found nor any long-bone changes seen in 3 babies. Two of the placentas were negative, and one was premature. No organisms could be found, but changes in the long bones were seen in one baby. The placenta was premature and probably positive.

The mothers of 2 babies received 7 or more treatments. The organisms of syphilis were not found in either of the babies. The long-bone changes were not present in one; the placenta was premature and negative. No roentgen ray examination was made of the other baby; the placenta was negative.

Placental Histology of Premature Live Babies Checked With the Long-Bone Changes (25).—The placental findings of 25 premature live babies were checked with the long-bone changes. The mothers of 4 of these babies received no prenatal antisyphilitic treatment. Long-bone changes were present in 3 babies and absent

in one baby. In the baby with no long-bone changes, the placenta was negative. The other 3 placentas were premature and probably positive, 2; and positive, 1.

Fifteen mothers had fewer than 7 treatments. Long-bone changes were present in 2 babies. One placenta was premature, and one was positive. There were no long-bone changes in 13 babies. Ten of the placentas were negative; one was premature and probably negative; one was premature and negative; and one was positive.

The mothers of 6 babies received 7 or more treatments. There were no long-bone changes in the babies and all six of the placentas were negative.

Placental Histology of Premature Stillborn Babies Checked With the Long-Bone Changes (126).—This study was made on 126 of the 146 premature stillborn babies. The mothers of 89 received no treatment. There were long-bone changes in 63 of the 89 babies. The placentas were negative in 15; probably negative, 1; premature, 8; premature and probably negative, 3; premature and probably positive, 18; premature and negative, 1; premature and positive, 4; positive, 12; and probably positive, 1. There were no long-bone changes in the other 26 babies. The placentas were negative in 8; premature, 5; premature and probably negative, 6; premature and probably positive, 3; premature and negative, 2; positive, 1; and probably positive, 1.

There were 32 mothers who received fewer than 7 treatments. Long-bone changes were found in 18 of the babies. The placentas were diagnosed: negative, 7; premature, 2; premature and probably negative, 1; premature and probably positive, 2; premature and negative, 2; premature and positive, 2; and positive, 2. There were no long-bone changes found in 14. The placentas were negative in 4; premature, 4; premature and probably negative, 2; premature and probably positive, 1; and premature and negative, 3.

Only 5 mothers received 7 or more treatments. There were no long-bone changes in the babies. Four placentas were negative, and one was premature and negative.

Abortions (123).—Babies weighing less than 1,500 gm. at birth and pregnancies reported as under seven months' gestation, without the birth weights, were classified as abortions. The placentas of 123 such issues were studied.

Abortions Born Alive (3): Only 3 of the 123 abortions studied were born alive. Two of them died, one immediately after birth. There is no record of the death of the third. In one case the mother had no treatment, the placenta was premature and probably positive. The mothers in the other two cases received fewer than 7 treatments. One placenta was negative, and the other was probably negative.

Abortions Stillborn (120): The mothers in 86 of the 120 stillborn abortion cases received no treatment. The placentas were negative in 24; probably negative, 1; premature and probably negative, 6; premature and probably positive, 24; premature, 13; premature and negative, 5; premature and positive, 7; positive, 4; and probably positive, 2.

Twenty-eight mothers received fewer than 7 treatments. The placentas were negative in 3; premature, 4; premature and probably negative, 4; premature and probably positive, 9; premature and negative, 4; premature and positive, 2; positive, 1; and probably positive, 1.

The mothers in 6 abortion cases received 7 or more treatments. One placenta was negative; 2 were premature; 2 were premature and probably negative; and 1 was positive.

Autopsies on Abortions (59).—Autopsies were performed in 59 of the 120 cases of stillborn abortions. The mothers in 49 of these cases received no treatment. The organisms of syphilis were found in the stained tissues of 33 aborted fetuses. Long-bone-changes were positive in all of these. Three placentas were negative; 5 were

premature; 15 were premature and probably positive; 2 were premature and negative; 5 were premature and positive; 2 were positive; and 1 was probably positive. There was one aborted fetus in which the organisms of syphilis were found, but no changes were seen in the long bones. The placenta was premature and probably positive. There were no organisms found nor any long-bone changes seen in 14. Nine of the placentas were negative; 3 were premature; 1 was premature and probably negative; and 1 was premature and negative. In one fetus the long-bone changes were thought to be positive, but no organisms could be found in the stained tissues. The placenta was probably negative.

The mothers of the other 10 aborted fetuses received fewer than 7 treatments. The long-bone changes were positive, and the organisms were found in 2 of the fetuses. One placenta was premature and probably positive, and one was probably positive. The organisms were found in the tissues of one aborted fetus, but no long-bone changes were present. The placenta was premature and probably positive. The organisms were not found, and there were no long-bone changes in 6 fetuses. One placenta was negative; 1 was premature; 3 were premature and probably negative; and 1 was premature and negative. In one fetus, the organisms could not be found, but long-bone changes were present; the placenta was negative.

Placental Histology of Stillborn Abortions Checked With the Long-Bone Changes (99).—The placental findings of 99 of the 120 stillborn abortions were checked with the long-bone changes.

Seventy-three mothers had no treatment, and long-bone changes were present in 51 of the 73 abortions. The placentas were negative in 5; probably negative, 1; premature, 7; premature and probably negative, 2; premature and probably positive, 23; premature and negative, 2; premature and positive, 6; positive, 3; and probably positive, 2. Long-bone changes were not present in the other 22 abortions. Fourteen of the placentas were negative; 3 were premature; 2 were premature and probably negative; 1 was premature and probably positive; and 2 were premature and negative.

Long-bone changes were found in 13 of the 22 aborted fetuses whose mothers received fewer than 7 treatments. The placentas were negative, 1; premature, 2; premature and probably positive, 7; premature and negative, 1; premature and positive, 1; and probably positive, 1. There were no long-bone changes in 9. One placenta was negative; 1 was premature; 3 were premature and probably negative; 2 were premature and probably positive; 1 was premature and negative; and 1 was premature and positive.

Long-bone changes were present in 2 of the 4 aborted fetuses whose mothers received 7 or more treatments. One placenta was negative, and the other was premature. There were no long-bone changes in the other two abortions; both placentas were premature and probably negative.

SUMMARY

The histologic examination of syphilis was attempted on 1,085 placentas of women with strongly positive blood Wassermann reactions.

The histologic examination of 679 placentas of live term babies, regardless of the treatment that the mother received during pregnancy, showed a positive or a negative diagnosis in 654. In only 25 was the diagnosis equivocal.

The placentas of 63 dead term babies were studied. The diagnoses were positive or negative in 45 and doubtful in 18. There were al-

most as many doubtful diagnoses in 63 placentas of dead term babies as there were in 679 placentas of live term babies.

The organisms of syphilis were found in 13 dead term babies in whom long-bone changes indicative of syphilis were present. One placenta was syphilitic, and one was not syphilitic. Eleven of the placentas were given doubtful diagnoses. In 2 dead term babies the organisms of syphilis were found; the roentgen ray examinations were negative. Both placentas were diagnosed negative. In 18 dead-term babies neither organisms nor long-bone changes were found (no roentgen ray examination was made of one baby). All the placentas were negative except one which was diagnosed premature and negative.

Roentgen ray examinations of the long bones of 101 live term babies were made. Long-bone changes indicative of syphilis were present in 6 of the babies. The 6 placentas were negative. There were 3 doubtful diagnoses in these 101 placentas; all the others were negative.

Roentgen ray examinations of the long bones were made of 54 dead term babies. The placentas of 22 babies with positive long-bone changes were examined. Six of the placentas were negative, 3 were positive; and 13 were doubtful. The placentas of the 32 babies in whom no long-bone changes were present were negative in 29; and doubtful in 3.

The attempt to diagnose syphilis of the placenta of 78 premature live babies resulted in a doubtful opinion in 20 of them, again, nearly as large a failure as was obtained in the 679 placentas of live term babies. The diagnostic attempt on the placentas of 142 premature dead babies resulted in doubtful diagnoses in 82.

There were 32 premature dead babies in whom the organisms of syphilis were found and the long-bone changes of syphilis present. The 32 placentas were examined. Eight were negative; 5 were positive; and doubtful diagnoses were made in 19.

There were 6 premature dead babies in whom the organisms of syphilis were found, but no long-bone changes were present. Only one of these placentas was diagnosed positive; the other 5 were diagnosed doubtful.

Roentgen ray examinations of the long bones were made of 25 premature live babies. Five of these showed positive long-bone changes. Two of the placentas were positive for syphilis, and 3 were diagnosed doubtful. There were no long-bone changes present in the other 20 babies. The placentas were negative in 17, positive in 1 and doubtful in 2.

Roentgen ray examinations of the long bones were made of 126 premature dead babies. Eighty-one babies showed positive long-bone changes. The placentas were negative in 22, positive in 14 and doubtful in 45. There were no long-bone changes seen in the other 45

babies. The placentas were negative in 16, positive in 1, and doubtful in 28.

A positive or a negative diagnosis of syphilis of the placenta was made in only 35 of the placentas of the 123 abortions studied.

The placentas of 86 stillborn abortions, the mothers receiving no prenatal antisyphilitic treatment, were studied. Doubtful diagnoses were made on 58 of them. The placentas of 34 stillborn abortions, the mothers receiving either more or less treatment, were examined. Doubtful diagnoses were made on 28. There were only 6 mothers in the series of 123 abortions who received 7 or more prenatal antisyphilitic treatments.

Both long-bone changes and the organisms of syphilis were found in 35 abortions. The placentas were examined and doubtful diagnoses of various kinds were made of 30. Organisms were found but no long-bone changes were seen in 2 aborted fetuses. Both placentas were diagnosed doubtful for syphilis.

Roentgen ray studies were made of the long bones of 99 stillborn abortions. Sixty-six showed positive long-bone changes. A diagnosis of syphilis was made on only 3 of the 66 placentas. Seven of the placentas were negative; the other 56 were doubtful. There were 33 abortions in this group in which no long-bone changes were present. Fifteen of the placentas were negative; the rest were doubtful.

Plass told me ten years ago that he believed that the antisyphilitic treatment of pregnant women had some definite influence on the histologic appearance of the placenta. This work seems to confirm that statement. The placentas of 272 mothers who received 7 or more treatments were examined. One placenta was positive. There were but 13 equivocal diagnoses in the group.

The more distant from term, the greater is the difficulty in making a histologic diagnosis of syphilis of the placenta. Dead babies seem to increase this difficulty, regardless of the duration of the pregnancy.

REFERENCES

(1) *McCord, James R.:* Am. J. Obst. & Gynéc. **18:** 597, 1929. (2) *McCord, James R.:* Tr. Am. Assoc. Obst., Gynec. & Abd. Surg. **42:** 265, 1929. (3) *Bromer, Ralph:* New England J. Med. **200:** No. 11, 1929. (4) *Hofbauer, J.:* Am. J. Obst. & Gynec., July, 1925: 1-14. (5) *Idem:* Personal communications. (6) *Plass, E. D.:* Personal communication. (7) *Wallich, V., and Levaditi, C.:* Ann. de gynéc. et d'obst. February, 1906. (8) *Holland, Eardley:* The Causation of Foetal Death, London, 1922. (9) *Moore:* Modern Treatment of Syphilis, Springfield, Ill., 1933, Charles C. Thomas. (10) *Williams:* Obstetrics, ed. 6, New York, 1930, 748, D. Appleton-Century Co. (11) *Pendergrass, E. P., and Bromer, Ralph S.:* Am. J. Roentgenol. **22:** 1, 1929.

50 Armstrong Street

A REPORT OF 565 VAGINAL HYSTERECTOMIES PERFORMED FOR BENIGN PELVIC DISEASE

N. Sproat Heaney, A.B., M.D., F.A.C.S., Chicago, Ill.

AT THE 1930 meeting of the American Gynecological Society during the discussion on the paper by Dr. George Gellhorn, "Vaginal Hysterectomy Under Local Anesthesia," I reported a series of 327 vaginal hysterectomies under ethylene anesthesia with 3 deaths. That report included both malignant and nonmalignant disease. I have eliminated the malignant cases from that series and now wish to report on a total of 565 vaginal hysterectomies for benign disease with two deaths, or a mortality rate of 0.35 per cent. This includes all cases operated upon since we first began using ethylene gas whether the patient received ethylene or another anesthetic, since, in this paper, I am making an analysis of an operation, not of an anesthetic. At the Presbyterian Hospital in Chicago, there is no cross file of cases according to operation, records being filed according to disease only. I began keeping a private cross file according to operations at the time we first began using ethylene anesthesia. For that reason this report includes only such cases as were operated upon since that time. Cancer carries with it its own peculiar operative risks both because of the nature of the disease and the extent and seriousness of any operation aimed at its cure. Hence, cancer cases are excluded from this discussion, except those discovered accidentally by microscopic examination postoperatively, cases in which cancer could not be diagnosed clinically previous to operation. In such instances the cancer could have no influence upon the operation or the convalescence of the patient, and, therefore, they were not excluded.

Vaginal hysterectomy is the operation of choice in my hands for the removal of the uterus except in cases in which it seems impossible of completion because of fixation of the uterus or because of an unusually large tumor. Thus far I have never had to abandon the vaginal route and complete the operation abdominally. Of the 565 patients 106 were nulliparas. In several instances fibroids extending to the umbilicus were removed piecemeal. Though I have failed to write in my tabulation book the frequency of morcellation in the entire series, I have noted that morcellation was resorted to sixteen times in the last 110 cases.

The age incidence is shown in Table I.

Table I

14 between ages of	25 to 29
179 between ages of	30 to 39
287 between ages of	40 to 49
65 between ages of	50 to 59
16 between ages of	60 to 69
4 between ages of	70 to 76

Table II shows the indications for operation.

It will be seen in Table II that a carcinoma of the cervix is reported associated with an ovarian cyst. The patient was fat and well past the climacterium. The uterus was removed because the cervix was badly scarred and to secure additional room for the removal of the cyst. Microscopic examination revealed cancer. It was not possible to diagnose this case either before or during operation; in fact, cancer was not suspected. Similarly in this series, though not suspected, 4 carcinomas of the cervix in situ, 4 carcinomas of the corpus uteri, 3 carcinomas of cervical polyps, and one carcinoma of the ovary were found. The ovarian carcinoma was the size of a walnut and could not be palpated in the presence of a fist-sized fibroid.

TABLE II

Fibromyoma of the uterus	294
Uncontrollable menorrhagia	110
Prolapsus of the uterus	71
Adenomyoma of the uterus	58
Persistent leucorrhea (uterine origin)	9
Sterilizing procedure	6
Retroversion	5
Uncontrollable dysmenorrhea	3
Prolapsus of the uterus with tubal pregnancy	1
Previous interposition operation producing bladder symptoms	1
Endometriosis of uterus and ovaries	1
Ovarian cyst and carcinoma of the cervix	1
Ovarian cyst	2
Stricture of cervix	2
Bilateral chocolate cysts of ovary	1

TABLE III

Hypertension, systolic blood pressure over 150	71
Secondary anemia, hemoglobin under 60	64
Nephritis or albuminuria	22
Pulmonary tuberculosis (arrested)	3
Splenomegaly	1
Diabetes	4
Mitral stenosis	2

The important associated physical complications noted are listed in Table III.

Previous to operation an attempt is made to get the patient into the best physical condition so that the operation may be as safe as possible. Abscessed teeth are removed and infected tonsils are drained or removed and healing allowed before hysterectomy is performed. Endocervicitis is treated, infected nabothian follicles are destroyed by the cautery and decubitus ulcers in prolapse cases are treated till healed before operation.

TECHNIC

Operative steps are as follows after the usual vaginal preparation: the vagina is swabbed out with Lugol's solution, the cervix is grasped with a bullet forceps and strong downward traction is exerted. Two cubic centimeters of obstetric pitu-

itary extract are injected into the paracervical tissue to reduce the bleeding. A transverse incision is made through the vaginal mucosa close to the anterior lip of the cervix. The vaginal mucosa and the attached bladder are then dissected free from the anterior wall of the uterus up to the plica vesicouterina, which is incised. A slender long-bladed retractor is inserted through this anterior colpotomy incision and the bladder held forward with the attached ureters. Next a transverse incision is made in the mucosa of the vagina behind the posterior lip of the cervix. A flap of mucosa is pushed back, the culdesac opened and a narrow long-bladed retractor inserted in the posterior colpotomy opening.

The anterior and posterior incisions are joined by a lateral incision on each side of the cervix and the mucosa pushed back an eighth of an inch. The retractors are widely separated and the left sacrouterine ligament is grasped firmly with a slender curved clamp. The ligament is cut mesially and the clamp removed as a ligature is anchored and tied about it. Next the clamp is placed on the lower portion of the broad ligament and the uterine vessels. After the severing of this portion, the clamp is again replaced by a ligature. In a similar way the right sacrouterine ligament and uterine vessels are ligated. The body of the uterus may now be delivered either anteriorly or posteriorly and freed by clamping and suturing the upper portion of each broad ligament. Each of these ligatures is cut long and held with a hemostat. The appendages are inspected by drawing them into view and any indicated procedure may be performed. A small pack is introduced to hold the intestines back while closing the incision. A suture is then passed through the right edge of the anterior vaginal cuff, taking several small bites of tissue on the denuded surface of the bladder and picking up the anterior fold of peritoneum. The ligature around the upper end of the broad ligament is pulled down, and the peritoneum from the bladder to the broad ligament is brought into view and is fed onto the suture. The suture is then passed around the ligature holding the ovarian and round ligaments to again ligate the vessels and continued down the broad ligament peritonizing as it goes. It is passed around the stump of the uterine vessels and of the sacrouterine ligament, thus ligating them again, then picking up the posterior flap of peritoneum and passing out through the posterior vaginal mucosal flap. This suture is firmly tied. It not only closes the right side of the vaginal vault, but anchors it to the round and broad ligaments, peritonizes and doubly ligates the ovarian and uterine vessels. The pack is now removed and the left side is sutured in the same way. The rest of the incision is closed with two or three interrupted sutures, picking up in succession, anterior vaginal wall, anterior flap of peritoneum, posterior flap of peritoneum, and posterior vaginal mucosa. The incision is tightly closed without drainage and a vaginal pack inserted for twenty-four hours. No local treatments are administered. The same bladder attention is given as after an abdominal hysterectomy. The patient is kept in bed for one week and is dismissed ordinarily on the tenth or eleventh day. The average hospital stay for all cases was 12.16 days.

The additional operative procedures performed are shown in Table IV.

TABLE IV

Posterior colpoperineorrhaphy	268
One or both tubes removed	103
One or both ovaries removed	87
Plastic on urethra for incontinence	71
Removal of bartholinian cyst	5
Removal of adenomyoma of rectovaginal septum	5
Repair of complete perineal tear	3
Repair of rectovaginal fistula	1
Repair of fistula in ano	1
Vulvectomy	1

The two fatal cases were as follows:

CASE 1.—Patient, operated upon because of fibromyoma and menorrhagia, died on the fifth day of peritonitis. Microscopic examination showed the uterine wall to contain myriads of microscopic abscesses. It was later revealed that the patient had had an exploratory curettement within a week of her entrance upon my service and had kept this to herself.

CASE 2.—Patient had had a previous operation on appendages. During the hysterectomy the adherent ileum was incised but immediately sutured. Patient died on the fourth day from intestinal obstruction. An operation for the relief of the obstruction was performed but too late to be beneficial.

Table V shows postoperative complications.

TABLE V

Temperatures over 100.6° F. for one or more days		198
Due to cystitis	32	
Probably due to wound infection	164	
Femoral thrombophlebitis	1	
Parotitis	1	

Postoperative Hemorrhage (4 cases).—One patient showed evidence of internal bleeding the day following operation. Laparotomy showed that a small aberrant artery near the round ligament had not been ligated. Postoperative transfusion was followed by an uneventful recovery. Three patients bled copiously from the vaginal vault shortly after dismissal from the hospital. One patient required suture and transfusion; the other two were controlled by light tamponade. All recovered promptly.

The bladder separates from the cervix and lower pole of the uterus usually quite easily. When, however, an endometrioma has invaded the anterior culdesac or a fibroid nodule distorts the base of the bladder, it may be impossible to loosen the bladder without entering it. If this occurs, interrupted fine catgut sutures through the mucosa with a supporting row of somewhat heavier interrupted catgut sutures through the muscularis and careful covering of the suture lines with the vaginal mucosa make a safe closure. The insertion of a retention catheter to prevent distention of the bladder and tension on the sutures is an invaluable aid in the repair of such defects. In this series of cases the bladder was entered three times. In no case was the convalescence disturbed and healing was complete in all three.

Considerable fear exists in the minds of those not familiar with the technic that the ureters may frequently be ligated or injured. If the bladder is separated well laterally and the retractor is shifted to that side being operated upon, the ureters will be held away from the field of operation. There is less danger of injury to the ureter when operating vaginally than by the abdominal route, for the uterine vessels are clearly exposed and can be clamped and ligated under the direct guidance of the eye. In this series no injury to the ureters was demonstrable in any case.

I have repeatedly removed completely adenomyomas of the rectovaginal septum and surgically treated associated disease of the ovaries through a vaginal incision without removal of the uterus. As a matter of fact, it is usually easier to dissect an adenoma from the rectum by the vaginal route than it is through an abdominal incision. In this series of vaginal hysterectomies 5 had associated adenomyomas of the rectovaginal septum. In one a tiny hole was made in the rectum; this hole was immediately closed and the patient had an uncomplicated convalescence. Otherwise there were no injuries to the rectum.

Some years ago it happened several times that some time during convalescence the vaginal vault opened and allowed the prolapse of a tube, which later healed in this position and produced much vaginal discharge. In this series I was completely free of this annoying complication until recently when I had this accident happen twice. In each case it was possible to place a ligature about the mesosalpinx and remove the tube with a small cautery without difficulty or more disturbance to the patient than is experienced in the removal of granulation tissue.

For the most part the convalescence of these patients was much smoother than one sees after the simplest laparotomy. On the average the disturbance was less than after an ordinary vaginal plastic operation. No patient suffered surgical shock. Only in a few instances did vomiting tend to become persistent. We have no record of any patient with acute dilatation of the stomach. The usual patient suffered but little and relished her breakfast the morning following operation.

Formerly vaginal hysterectomy was much in vogue but with the development of abdominal surgery and especially because of the overemphasis placed upon so-called chronic lesions of the appendix, gynecologists gradually deserted the vaginal route in order to remove appendices, sever Jackson's membranes, stitch up prolapsed cecums, and do much other questionable surgery. Now that these conditions have been evaluated and the harmlessness of most of these deviations has been established, a new race of gynecologists has been reared which has relatively little or no familiarity with the vaginal attack on pelvic lesions. It is the purpose of this paper to show again how low the mortality and morbidity of vaginal hysterectomy may be with the hope that this operation may find a place in the operative armamentarium of every gynecologist.

111 East Pearson Street

THE MANAGEMENT OF OCCIPUT POSTERIOR

A Further Consideration of Manual Rotation

W. C. Danforth, B.S., M.D., F.A.C.S., Evanston, Ill.

(From the Department of Obstetrics and Gynecology of the Northwestern University Medical School and of the Evanston Hospital)

THREE years ago I described a method of manual rotation for use in cases in which the occiput fails spontaneously to undergo anterior rotation. This has been of great service to my associates and myself, and I wish at this time to present a further consideration of this procedure based upon a larger number of cases. Many of the recent publications upon the management of occipitoposterior positions advocate a rather active form of treatment, intervention being carried out at a stage of labor which is too early to permit spontaneous anterior rotation to occur. In this study about 70 per cent of posterior positions spontaneously became anterior. It is possible that this number would be slightly increased were all cases left alone a still longer time.

The dread with which posterior positions are regarded by many physicians is probably based upon the fact that, in the hands of many practitioners of deficient obstetric training only those cases are recognized as posterior which fail to rotate and never require operative treatment. Those which rotate spontaneously, nearly three-fourths of the entire number, escape recognition. As it is the smaller number which do not rotate anteriorly which cause trouble, the condition is regarded with a greater dread than it actually merits.

In the management of these, the total of maternal and fetal injury still remains far too great, and the loss of infant life as a result of various forms of operative delivery is still far larger than it should be. A large amount of morbidity follows the traumatic deliveries to which these women are sometimes subjected. Much, if not most of this, may be avoided.

For the purpose of this study I have discarded all cases upon the ward service and have not considered the private work of my associates and have taken only private cases delivered by myself in the past nine years. These number 1,565. In 443, or 27.1 per cent, of these a posterior position was present. This is a larger incidence than appears in many reports. This, I believe, may be explained by the fact that, as all were private cases, the diagnosis of posterior position was made early in labor. In many services, in which observations are made and recorded by internes, the cases in which anterior rotation

occurs spontaneously are recorded as anterior positions, and the primary posterior position escapes recognition.

During the first stage of labor no interference should be attempted unless some unusual condition demands. Dilatation should be allowed to proceed normally and should be accomplished by the forces of nature. It is a clinical fact that labor in the presence of a posterior position tends to proceed more slowly, and the obstetrician should not allow the woman to become exhausted physically or nervously. The management of labor in occipitoposterior positions begins in the first stage. Pain must be relieved during the first stage by some effective method. The woman should be brought into the second stage with her physical and nervous forces as nearly intact as possible. If possible the membranes should be preserved intact until the first stage is complete or nearly so. Only rarely will completion of dilatation manually or by Dührssen's incisions be required. These procedures should only be used after careful weighing of indications.

It is probable that in many, if not in most, cases, the head enters the pelvis in the transverse position. As descent proceeds, the occiput rotates anteriorly or posteriorly, most frequently the former. The most dependent portion of the presenting part tends to rotate anteriorly. Flexion is often deficient in posterior positions and this may explain the tendency of the occiput in these cases to turn toward the back.

TABLE I

Total number	1,565	
Posterior positions	443	(27.1%)
R.O.P.	386	
L.O.P.	57	

TABLE II. MANAGEMENT

Spontaneous rotation and delivery	125	69.03%
Spontaneous rotation and forceps	175	
Manual rotation and forceps	98	
Version only	14	
Failure of manual rotation and forceps	11	
Forceps rotation	2	
Cesarean (for indications other than posterior position)	13	

Certain variations in the pelvis may increase the likelihood of a posterior position. These have been discussed by Thoms and by Caldwell and Moloy. Melhado suggests that possibly some alteration in the uterus itself may play a part and refers to its development from the bilateral müllerian tracts of which one may have developed less well than the other. It is not desired to discuss the mechanism extensively.

At the beginning of the second stage of labor, the obstetrician must observe the further progress of labor carefully. It is desired that, if possible, the descent and anterior rotation of the head should proceed

normally and spontaneously. The labor must not be permitted to proceed, however, so long a time that a contraction ring develops. The second stage should never be allowed to go on longer than three hours, and in my own work I rarely wait more than two hours. In our experience contraction rings have developed in less than two hours, but this is unusual. If labor is permitted to continue much over two and a half hours, the danger of the development of a contraction ring becomes notably greater.

If descent and anterior rotation occur, either spontaneous delivery or a simple outlet forceps terminates the labor. This occurred in 300 cases, or 69.03 per cent. It is with the remainder that I am concerned in this report.

My procedure of election is a form of manual rotation which has been so useful that I wish again to urge its merits. In most methods of manual rotation which have been described it is necessary to use

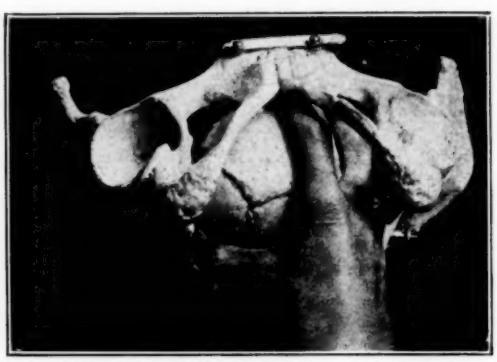


Fig. 1.—The head is grasped by the hand with the fingers widely spread out. Rotation is assisted by the opposite arm pushing upon the shoulder.

either the left or the right hand to perform the rotation, the choice of hands depending upon the side upon which the occiput lies. This brings with it the necessity in some cases of holding the occiput in the anterior position by means of tenacula, as, if the hand is removed, it tends to resume its original position. Again, in some cases the right blade of the forceps must be introduced first. This necessitates an awkward readjustment of the blades before they can be locked. By the method which I have used, it has been possible to perform the rotation in all cases with the right hand and to introduce in all cases the left blade of the forceps first, thus obviating the tendency of the head to turn to its original position and rendering it possible always to use the left blade first.

After the rotation is completed with the hand, the thumb is withdrawn leaving the fingers of the right hand in contact with the lateral aspect of the head. In the more frequent R.O.P. this contact of the fingers should be against the cheek or jaw of the infant. If the rota-

tion has been done from a left posterior position, it should be against the lateral aspect of the occiput. This prevents the occiput from turning back to its original posterior position.

Rotation should not be attempted before dilatation is complete, nor should it be done until the head is well engaged. If interference becomes necessary before engagement has occurred, some other procedure must be chosen. If it is necessary for the head to mould before engagement can occur, labor must go on until this is brought about. The elongation of the head which is found in marked moulding, often causes an inexperienced obstetrician to assume that the head is lower in the pelvis than it really is. This error is particularly likely to occur if a well-developed caput succedaneum is present as this increases the length of the moulded head and, consequently, its apparent depth

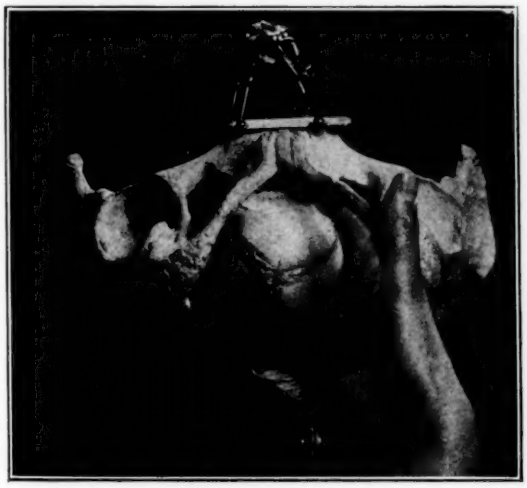


Fig. 2.—Rotation is complete. The thumb is withdrawn, the fingers remaining to prevent the occiput from resuming the posterior position and to guide the forceps.

in the pelvis. If too much time is consumed in the process of moulding and engagement, it may be wiser to adopt some other means of delivery. If after two, or at most two and a half, hours of active second-stage labor rotation has not occurred, or only partial rotation to a transverse position has taken place, or if, as occasionally may happen, the occiput has rotated into the hollow of the sacrum, active interference is indicated.

The position of the head should always be accurately determined by the palpation of the posterior ear in order that one may begin with an accurate knowledge of the position.

The right hand then grasps the head, spreading the fingers as widely as possible and pronating or turning the hand as far to the left as possible in order that, when the forearm is again supinated or turned to the right the head may be caused to rotate through as much of the

necessary are as possible. It may be necessary to grasp the head a second time if the maneuver is not completed with the first grasp. If the thin fetal skull gives under the fingers, the grasp may be shifted. The position should be slightly overcorrected so that the occiput at the conclusion of the maneuver will lie slightly to the left of the midline. This is to allow for some tendency to turn back. If the head will not rotate easily at the level at which it lies at the beginning of the maneuver, it may be necessary to displace it upward. In some cases this has been done to the point of complete disengagement. This brings with it the risk of prolapse of the cord. This occurred in only one case. If cord prolapse occurs, it is best to proceed to immediate version.

While the rotation of the head is being carried out with the right hand, it is of material advantage to push the shoulder of the infant

Fig. 3.—The right blade is introduced first according to the law of the forceps. Delivery is completed as in ordinary forceps.

toward the maternal midline by pressure of the left hand exerted through the right side of the mother's abdomen. After completion of rotation the hand of the operator may be replaced by that of an assistant or a nurse who will maintain pressure until the forceps have grasped the head and prevented resumption of the posterior position. In an occasional case, if the head is difficult to move, the right hand may be passed beyond the head and the shoulder may be pushed around. This is only exceptionally necessary.

If the posterior position is a left one, the same maneuver serves. The movements are reversed, and the abdominal hand pulls rather than pushes the shoulder toward the midline.

It should be emphasized that for successful accomplishment of rotation the uterine musculature must be relaxed. This requires an ether anesthetic. To accomplish rotation when the fetal body and head are

firmly grasped by the uterine musculature is often impossible, and, in any event, requires a very much greater expenditure of force.

It is remarkable with what ease the head in the corrected position will sometimes come down. Even when disengagement of the head has been necessary reengagement readily takes place. This is easily understood as the moulding which has already occurred, if a slight disproportion existed, has caused the head to fit the pelvis. It should be emphasized again that, if moulding is needed, it should take place before rotation is attempted.

If manual rotation fails, or if after accomplishing it, it is difficult to bring down the head with the forceps, version should be performed. One should not persist in attempting to do something which is obviously difficult and which will require much expenditure of force.

In 1,565 cases there were 443 posterior positions, or 27.1 per cent. Of these 386 were right posterior and 57, left posterior. Of the posterior positions, 125 rotated and delivered spontaneously. In 175 other cases anterior rotation and descent occurred, and delivery was completed by a simple outlet forceps. In 69.03 per cent of the total number spontaneous anterior rotation and descent took place, followed either by spontaneous delivery or outlet forceps. This seems to be a strong argument in favor of at least a degree of conservatism.

The procedure described above was carried out successfully in 98 cases, delivery being immediately accomplished by forceps. In 11 additional cases, rotation failed, and version was performed. In 14 cases version was performed as a primary procedure, manual rotation not being attempted. In a recent case in which version was performed as a primary procedure, as the membranes had ruptured early in labor and the fluid had drained away, 600 c.c. of weak sterile green soap solution was injected into the uterine cavity to replace the absent amniotic fluid. This procedure has been suggested by Piper and seems to have a field of usefulness in this class of cases. In this case the version seemed quite definitely to be facilitated by the presence of the soap solution. In two cases forceps rotation was done. In twelve cases in which the occiput lay in one of the posterior quadrants, cesarian section was performed. In none of these cases was the posterior position the indication for abdominal delivery. It was merely an incidental finding.

The morbidity in this series has been estimated by a very exacting standard, every patient in whom a temperature of 100.4° F. appeared at any time being placed in the morbidity list. If the standard suggested by the American College of Surgeons and the British Medical Association were followed, the number of cases in the morbidity list would be much smaller. This standard demands that a patient should be considered as febrile if a temperature of 100.4° F. appears on any two consecutive days excluding the first. By the more rigorous stand-

ard stated above there were 14.8 per cent of cases included, a total of 65. In 17 cases manual rotation had been performed; in 8 cases, version, while in 34 delivery was spontaneous or by simple outlet forceps.

TABLE III. MORBIDITY (ONE RISE TO 100.4° F.)

Total number	65	14.8%
Manual rotation	12	
Version	8	
Spontaneous delivery or low forceps	34	

No maternal loss of life occurred in this series. Only one infant was lost. This was a premature seven months' infant which was delivered spontaneously. This case was included in the previous report made of this procedure. No infant deaths occurred in the additional cases which appear in this communication. The great majority of infant deaths which occur in operative deliveries are the result of intracranial hemorrhage. It would appear that this complication is well avoided by this method of delivery. As has already been explained, if the soft fetal skull is felt to give under the rotating hand the grip may be shifted so as to minimize cerebral trauma to the greatest degree. Forceps are not applied until the head is in the position in which it may be caused to advance with the least application of force.

TABLE IV. MORTALITY

Maternal	0
Fetal (one premature child)	1

One noteworthy advantage of this procedure is the absence of high vaginal tears which may accompany forceps rotation. After extended experience, this method has been found so useful that its use is again suggested. In our own work it has been so useful that the posterior position at present causes little anxiety; as in the great majority of cases of failure of rotation or of partial rotation into the transverse position, the situation can be successfully met.

I would emphasize again the prerequisites named in my first communication:

1. The head must be engaged. If moulding is needed, interference must not be attempted until it has taken place.

2. Interference must precede the development of a contraction ring. For this reason the second stage must not be allowed to continue too long.

3. Relaxation of the uterine musculature is essential. Ether anesthesia is needed. This is one of the few remaining conditions in obstetrics in which ether anesthesia is still essential.

636 CHURCH STREET

THE INNOCUOUSNESS OF RUPTURE OF THE MEMBRANES EARLY IN NORMAL LABOR

E. L. King, M.D., New Orleans, La.

IT IS with some trepidation that I present this paper, fearing on the one hand that the subject may be considered to be so elementary that it does not merit discussion, and on the other hand being concerned lest the idea expressed by the title may be deemed to be unsound and hence worthy of vigorous disapproval. But I feel that this topic should be considered in view of various reports in the literature of the past few years bearing on the questions of spontaneous and artificial rupture of the membranes before and early in labor and the induction of labor by artificial opening of the amniotic sac. It is possible that some of our ideas may need a little readjustment. I wish to emphasize the use of the term "normal" in the title; this point, I trust, will be made clear in the discussion.

Let us consider the changes occurring in the first stage of labor. The obliteration of the cervix and the dilatation of the external os is brought about chiefly by two interacting mechanisms. One consists of traction exerted on the fibers of the cervix by the longitudinal fibers of the outer muscular layer of the body of the uterus, thus pulling the cervix upward to form a downward extension of the lower uterine segment. Shears[1] states that these longitudinal fibers are inserted into the circular fibers of the internal os, and that by their eccentric pull dilatation of the os is gradually effected, and it is drawn up over the presenting part, that is, that the head is not pushed through the cervix, but the latter is drawn upward over the head. This mechanism has been known for years, but of late it has been accorded increasing importance. The other factor concerned in the first stage is the familiar one of the hydrostatic action of that portion of the amniotic fluid found between the presenting part and the cervix, commonly called the "bag of waters." Great significance is assigned to this phase of the mechanism by most writers, and it is generally considered to be the most important factor.

Williams[2] stated that the changes in the cervix are brought about almost entirely by the action of the bag of waters; the same view is set forth in the work of Edgar and Vaux.[3] DeLee,[4] Shears,[1] Harper,[5] Eden and Holland,[6] Tweedy, Wrench, and Solomons,[7] Bumm,[8] Bland,[9] Harris,[10] and others consider both mechanisms to be of importance but with the action of the membranes playing the major rôle. It is generally considered that the bag of waters has important functions in protecting the head of the child from injurious pressure, in insuring a uniform elastic dilating wedge, and in minimizing the trauma to the cervix.

Rupture of the membranes prior to or early in the first stage of labor is classed as premature and is considered to be an unfavorable development by laity and profession alike. The phrase "dry labor" is usually employed to designate all such cases, but the term is used in a restricted sense by some writers.

Thus Edgar and Vaux[3] and Bland[9] apply the term only in those cases in which practically all the fluid has drained away. Harper[5] restricts this designation to those instances of rupture before moderately advanced dilatation of the internal os; in many cases of rupture of the membranes before the onset of pains he found that the internal os was already completely obliterated, and to these he would not apply the designation "dry labor." DeLee,[4] Williams,[2] and others place all cases of rupture of the membranes before or early in labor in this category. Many disadvantages and dangers are ascribed to this condition, such as prolonged, painful dilatation of the cervix, prolonged labor, increased percentage of operative interference, increased danger to the child, prolapsed cord, edema of the cervix, lacerations, infection, etc. The various textbooks are practically unanimous in agreement on these points.

In contrast to these views we find reports of series of cases of "dry labor" in which the course of labor was not atypical, with complications conspicuous by their absence.

Thus Brodhead[11] reports 182 private cases, in 80 per cent of which the membranes ruptured before labor began (in 1 case one month elapsed), while in 102 the rupture occurred at the onset of or early in labor. In 16 patients with membranes ruptured for 24 hours or more before the onset of labor, the average duration of labor was 16 plus hours for the 8 primiparas and 7 plus hours for the 8 multiparas. In the whole group of 182 the average length of labor was 13 hours 42 minutes for the primiparas and 7 hours 42 minutes for the multiparas. The majority of the primiparas were delivered by elective low forceps, not necessitated by the premature rupture of the membranes. Ten cases of persistent right occipitoposterior position were encountered but were not ascribed to the dry labor. There were 3 fetal deaths in the 107 primiparous cases, in one of which the dry labor could be considered as playing a part. The only fetal death in the 75 multiparas was that of a baby dying in utero several days before delivery. There was no maternal morbidity or mortality. The author concludes that, in the absence of other abnormal conditions, dry labor should be attended by no harmful results to mother or child. Dorman and Lyon[12] studied 270 cases, in which the membranes had ruptured twelve or more hours before the onset of labor. The most constant causative factor seemed to be pelvic deformity, but they also considered unusual rigidity of the cervix from previous injury or infection to be a factor in some cases. In 25 patients with membranes ruptured from 30 to 120 hours, the average duration of labor was 12½ hours; they concluded that the length of time the uterus had drained did not appear to affect the duration of labor unfavorably, nor to increase the risk to mother or child. There was an increase in the maternal morbidity, one maternal death from infection, and an increased fetal mortality rate, i.e., 8 per cent, as compared to the average for the hospital of 5.5 per cent. Norris[13] reported 196 cases of dry labor and inclined to the view that the condition is abnormal and unfavorable. Labor developed within 6 hours in 70 per cent of his cases. One hundred and six delivered spontaneously, the average time of labor being eleven hours, thirty-seven minutes, 50 per cent delivering in six hours or less; 90, or 46 per cent, were delivered by various operative procedures. The maternal morbidity was 24 per cent; there were no maternal

deaths, and the fetal mortality in cases at term was 5.5 per cent. Polak[14] in a general review of the subject quoted no figures but inclined toward a pessimistic view of the situation. He stated that "early rupture of the membranes . . . always prolongs labor." In cases with no disproportion, he advised a vaginal bag or a pack when cervical dilatation was not satisfactory; in patients with minor disproportion, low section was advocated if there was no progress after twelve hours of labor.

Randall[15] reported 88 cases (56 primiparas and 32 multiparas), constituting 12.5 per cent of 700 patients delivered at the Mayo Clinic. In 57 rupture occurred before the onset of labor; in 31, at the onset of or very early in labor. The average duration of labor was 17 hours in the primiparas and 10 hours in the multiparas. In 16 primiparas and 5 multiparas labor lasted longer than 20 hours, but in each instance factors other than dry labor were responsible. Fifty-eight were delivered spontaneously, and 30 (28 primiparas and 2 multiparas) were delivered by operative measures. There was no note as to the fetal mortality. The author concluded that, if conditions are otherwise normal, no particular difficulty is to be expected, and labor is not prolonged.

Quigley,[16] in a study of pregnancy and labor in elderly primiparas (35 years or more), noted dry labor in 82 out of 237 cases. The average length of labor in these patients was 11.6 hours, while in the entire series it was 15.3 hours. The percentage of spontaneous labor was the same (35.5 per cent); there were fewer cesarean sections and more forceps deliveries than in the other patients.

Margaret Schulze[17] presented a comprehensive and detailed report of 604 cases of dry labor occurring in a series of 6,500 deliveries (9.3 per cent), considering only those patients in whom rupture of the membranes occurred prior to or at the onset of labor. It was noted more frequently in patients with abnormal presentations. In contracted pelves, rupture of the membranes was frequent in early labor, but it did not occur prior to labor. In 224 cases, pains developed at once, in 57 there was a delay of twenty-four hours or more; in 26 cases there was a delay of three to nineteen days. The length of labor was shorter than the average for the patients with intact membranes, the first stages being chiefly affected. The average of the first stage was 12.1 hours for primiparas and 7.1 hours for multiparas, with second stages averaging 1.82 hours and 0.9 hour, respectively. In 8.4 per cent of the patients labor lasted over twenty-four hours, as contrasted with 12.4 per cent in 500 consecutive cases reported from the same clinic by Slemons. In the majority of these patients with prolonged labors, other factors contributed to the dystocia. The percentage of operative deliveries was rather high, but two-thirds of the patients so delivered had one or more causes for the dystocia other than the premature rupture of the membranes. There was no case of cervical laceration severe enough to require suture. There was no maternal mortality, but the morbidity was increased from 13.5 per cent to 17 per cent, higher still in cases in which the membranes had ruptured over twenty-four hours before the onset of labor, or in which labor had lasted over twenty-four hours. The fetal mortality was 5 per cent, but in the 409 cases in patients with normal pelves and occipitoanterior positions it was 1.2 per cent. The author concludes that in the absence of other complicating factors, labor is not prolonged (but rather, shortened), and there is no increased risk to mother or child.

These few reports make it clear that premature rupture of the membranes is not necessarily followed by dystocia, and it appears that when such develops, it is usually due to some abnormality independent of the loss of the amniotic fluid. In fact, in many cases there is very little draining away of this fluid, only that portion between the pre-

senting part and the cervix being lost. The abnormality present may be the cause, rather than the effect of the early rupture of the membranes.

Turning now to the question of the deliberate rupture of the membranes prior to or early in labor, we find that this method has been employed for hundreds of years for the induction of labor.

Fitzgibbon[18] has recently recorded his preference for this procedure, claiming that its efficiency is due to the pressure of the presenting part on the cervical ganglia, especially when some of the fluid is allowed to escape slowly, in order to permit the presenting part to engage more deeply. Slemons' method of preceding the rupture by castor oil, quinine, and an enema is probably more widely employed in this country at present than any other technic. It is interesting to note that while Williams was pessimistic regarding spontaneous premature rupture of the membranes, he was an enthusiastic advocate of this method of inducing labor. He stated that in 19 cases out of 20 pains developed in a few hours, and the labor usually progressed rapidly. He felt that the method was without danger to mother or child provided the head was engaged. In 1931, Guttmacher and Douglas[19] reported from Williams' clinic the results in 120 cases of induction by this procedure. In one series they employed in addition the Hofbauer intranasal application of pituitary extract; in the next series this was omitted; and in the third series only rupture of the membranes was performed without preliminary medication. In the first two series the latent period (i.e., the time before the onset of labor) was much shorter than in the third series, but the pituitary extract in the first series had little effect in further shortening this latent period. They found that labor was shorter than in normal cases by 73 per cent in the 61 primiparas (average duration 10.15 hours as against 17.59 hours), and by 116.4 per cent in the 58 multiparas (5.43 hours as compared to 11.75 hours in the total series of the hospital). In primiparas and multiparas alike, both stages were shortened, and this could be ascribed only to the rupture of the membranes. The latent period was less than four hours in 102 cases, and over four hours in the remaining 18. There were 3 cases of unsatisfactory labor, with slow onset and unsatisfactory progress; the other 117 were normal. There was no relationship between the amount of fluid lost at the time of rupture, the period of the pregnancy, or the size of the child, and the length of the latent period. If the cervix was partially dilated, the latent period was shortened, but not the duration of the labor. On the other hand, if the cervix was long and undilated, both the latent period and the labor were prolonged. In this series there was no increase in maternal morbidity (on the contrary, the rate was about one-half that usual in the clinic); there was no maternal death; there was no increase in operative interference; and the fetal mortality rate was 5.88 per cent, only a trifle higher than the rate of 5.16 per cent for the total series of the hospital. In 2 of the 7 babies lost, the induction might have been partly responsible for the outcome, but not in the other 5. In a separate series of 100 cases of spontaneous premature rupture, the latent period was four times longer in the primiparas and twice as long in the multiparas; the labors were a trifle longer, but still the average was much lower than for the total hospital series. In this series also the fetal mortality was not increased, being 5 per cent, and there was no increase in the operative interference or in the maternal morbidity.

Kreis,[20] writing from the clinic of the late Professor Schickele, in Strassbourg, is of the opinion that the bag of waters has little or no effect on the effacement of the cervix or on the dilatation of the external os, but that these changes are due to the previously mentioned action of the longitudinal fibers of the uterus on the

fibers of the cervix, which are pulled up into the lower uterine segment. He noted that in many cases, some without osseous dystocia and some with slightly contracted pelves, there was no engagement of the head, apparently because of the excessive amount of the forewaters and insufficient effacement of the cervix. Artificial rupture of the membranes brought about engagement and delivery in most instances, except in an occasional case of contracted pelvis, in which low cesarean section was performed after failure to secure proper progress. In order to test out these ideas as to the mechanism of dilatation, rupture of the membranes was performed in all cases admitted in labor, the only requirement being that in primiparas the cervix be effaced but not necessarily entirely so in multiparas. According to Harper, the term "dry labor" would not be applicable here. There was generally a latent period of varying duration, then an acceleration of the rhythm of the contractions and an increase in their duration. In some cases, what was called "collapse" of the external os developed, due to failure of the presenting part to descent against it, and in others a spasm of the external os developed (but not more frequently than in normal labor); this was thought to be due to faulty innervation and was always relieved by spasmalgine. This routine rupture of the membranes was later reported in detail by LaHaye,[21] who compared the results in 761 cases so treated with those in 1,893 cases pursuing the normal course. The average duration of the labors was materially shortened, there was no increase in the operative interference or in the fetal mortality, and the maternal morbidity was the same in both series.

Personal experience and the results obtained in my obstetric service tend to agree with the various findings above noted. I am not greatly worried about premature rupture of the membranes, provided that a careful study of the case shows that no abnormal condition is present. I feel that we can all agree that in the presence of disproportion, malpresentation, etc., premature rupture of the membranes is a complicating factor which cannot be disregarded. The induction of labor by the Slemons' method is preferred by us, and we continue to be surprised by the usual ease and rapidity of the labors; an eight-hour labor in a primipara is not uncommon. Great care must be exercised that the method be not employed in cases of disproportion or malpresentation; we prefer to use it only in normal anterior cephalic positions. A. G. King[22] recently reported from my service the results in 200 cases of deliberate rupture of the membranes early in labor in normal vertex cases, together with the results in 100 cases of spontaneous rupture as compared to 200 cases which were allowed to proceed normally. The labors were shortened by about one-third; the percentage of cases subject to interference was less (8.6 per cent as compared to 12.5); and the morbidity was lower (17.6 per cent as against 28 per cent). The fetal mortality was 3, one occurring in the group of spontaneous ruptures, none in the cases in which the membranes were artificially ruptured, and 2 in the 200 cases of intact membranes.

What are we to conclude from these various observations? Shall we say that all that has been written and said about dry labor in the past is wrong? Shall we practice and teach routine early rupture of the membranes? Not at all. I feel that what we should realize is that

the dystocia credited to dry labor is generally due to other complicating abnormal conditions, which occasion the premature rupture of the membranes; this rupture is a further complication in such cases. We should further realize and teach that premature rupture of the membranes in the absence of other complications is not a cause for undue alarm, that one should not resort to meddlesome midwifery, and that above all strict asepsis is necessary. In spite of the interesting observations of Kreis[20] and LaHaye,[21] apparently substantiated by our small series of 200 cases, I see no good reason for, and many against, the rupture of the membranes early in normal labor. The less we interfere with the normal progress of labor, so long as it is normal, the better for all concerned. But it is comforting to feel that, in normal labor, early rupture of the membranes, should it occur, is fairly innocuous and is not greatly to be feared.

REFERENCES

(1) *Shears, G. P.:* Obstetrics, Normal & Operative, Philadelphia, 1920, p. 112. (2) *Williams, J. W.:* Obstetrics, New York and London, 1930, D. Appleton Company, p. 816. (3) *Edgar, J. C., and Vaux, N. W.:* Obstetrics, Philadelphia, 1926, pp. 288-424. (4) *DeLee, J. B.:* Principles and Practise of Obstetrics, Philadelphia, 1933, W. B. Saunders Co., pp. 126-129 and 697. (5) *Harper, P. T.:* Clinical Obstetrics, Philadelphia, 1930, F. A. Davis Company, pp. 10-13. (6) *Eden and Holland:* Textbook of Obstetrics, New York, 1925, The Macmillan Company, pp. 210-215. (7) *Tweedy, Wrench, and Solomons:* Practical Obstetrics, London and New York, 1925, pp. 24, 25. (8) *Bumm, E.:* Grundriss zum Studium der Geburtshülfe, Munich, 1922, pp. 175-188. (9) *Bland, P. B., and Montgomery, T. L.:* Practical Obstetrics, Philadelphia, 1932, F. A. Davis Company, pp. 315-326 and 472. (10) *Harris, J. W.:* Curtis' Obstetrics & Gynecology, vol. 1, Philadelphia, 1933, W. B. Saunders Company. (11) *Brodhead, G. L.:* New York State J. Med. **24:** 801, 1924. (12) *Dorman, F. A., and Lyons, E. C.:* Am. J. Obst. & Gynec. **1:** 595, 1921. (13) *Norris, C. C.:* Am. J. Obst. & Gynec. **19:** 500, 1930. (14) *Polak, J. O.:* Am. J. Obst. & Gynec. **5:** 488, 1923. (15) *Randall, L. M.:* Minnesota Med. **8:** 525, 1925. (16) *Quigley, J. K.:* Am. J. Obst. & Gynec. **21:** 234, 1931. (17) *Schulze, Margaret:* Am. J. Obst. & Gynec. **17:** 20, 1929. (18) *Fitzgibbon, G.:* J. Obst. & Gynec. Brit. Emp. **38:** 495, 1931. (19) *Guttmacher, A. F., and Douglas, R. G.:* Am. J. Obst. & Gynec. **21:** 485, 1931. (20) *Kreis, J.:* Gynéc. et obst. **17:** 421, 1928; Bull. Soc. d'obst. & de gynéc. **18:** 78, 1929. (21) *LaHaye, P.:* Rev. franç. de gynéc. et d'obstét. **25:** 657, 1930. (22) *King, A. G.:* Deliberate Rupture of the Membranes Early in Labor, Am. J. Obst. & Gynec. **27:** 576, 1934.

Maison Blanche Building

Ueno, J.: A Study of the So-called "Sphincteric" Apparatus of the Fallopian Tube, Japanese J. Obst. & Gynec. **16:** 562, 1933.

The author denies the existence of a true sphincter apparatus in the fallopian tube. The phenomenon of "isthmospasm" does not arise from the constriction of the circular muscle in the tube but from simple contraction of the muscle in the isthmic part of the uterus. In other words this phenomenon is due to contraction of a special part of the uterus.

J. P. Greenhill.

DEMONSTRATION OF THE LYMPHATIC CIRCULATION IN THE PELVIS OF THE LIVING WOMAN BY THE ROENTGEN RAYS

GEORGE GELLHORN, M.D., F.A.C.S., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine and the Barnard Free Skin and Cancer Hospital)

IN THE course of a radical abdominal hysterectomy for cancer of the cervix one occasionally finds the lymph glands in the pelvic cellular tissue in surprisingly large numbers and at quite unexpected places. Such observations are at variance with the pictures of the pelvic lymphatic system in our textbooks. Further study of these pictures reveals that they are based largely on descriptions and illustrations furnished by Poirier in 1889 and even before that, by Sappey in 1874. Very little work has been done since to verify the studies of these older French anatomists.

Practically all previous data had been acquired from the cadaver by dissection or injection, but I endeavored to obtain some information in the living woman by injecting into the pelvic lymphatic circulation solutions which would leave a shadow on the x-ray plate.

For purposes of control a picture was taken in each case before the experiment was begun. As to the injection itself, the technic employed in the first five cases was simply that used for local anesthesia in vaginal hysterectomies, as described in my paper on this subject.[1] A very small amount of solution was injected into the parametria and between the leaves of the broad ligament, and then x-ray pictures were taken at intervals of from one to two or three days, to observe the behavior of the intraligamentous deposit. The first attempts with a sterilized suspension of Chinese black failed to show any shadows. Aqueous solutions of bismuth were so quickly taken up by the lymphatics and carried off out of the pelvis that even three hours after injection no imprint was made on the photographic plate. A suspension of bismuth in oil such as is used in the treatment of syphilis, on the other hand, gave a massive shadow, but the resorption was so slow that no marked changes could be seen from day to day, and even after three months there was practically no diminution of the original deposit.

In all subsequent experiments iodized oil was used for the injections.

In the first of these cases, in which 1 c.c. was injected on each side, the gradual diminution of the oil deposits and the extension toward the iliac and later the lumbar glands can be seen (Fig. 1). Two months after the injection I performed on this patient an abdominal hysterec-

tomy for fibroids without noticing any peritoneal or other irritation in the pelvic cavity. *This point deserves special mention in order to prove that the experiment is not harmful.* None of the eight patients thus far investigated complained of pain during the injection or after they had wakened from their "twilight sleep," and all left the hospital within 6 or 8 hours.

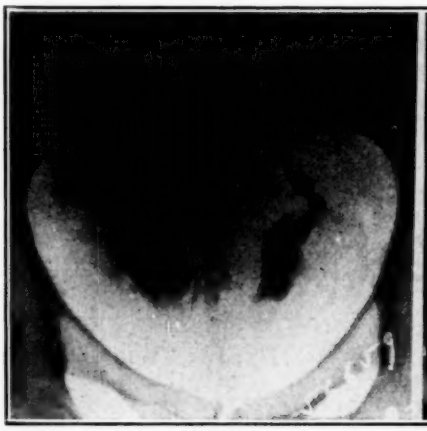


Fig. 1.

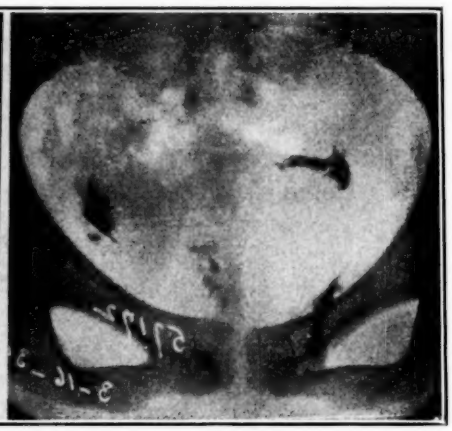


Fig. 2.

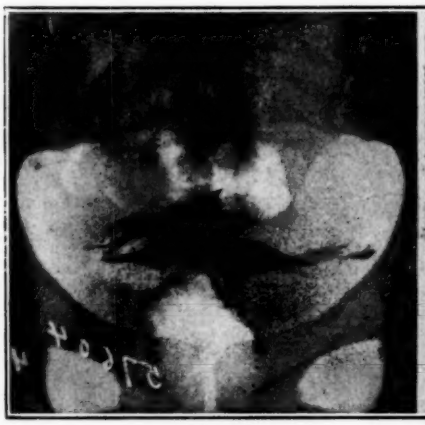


Fig. 3.

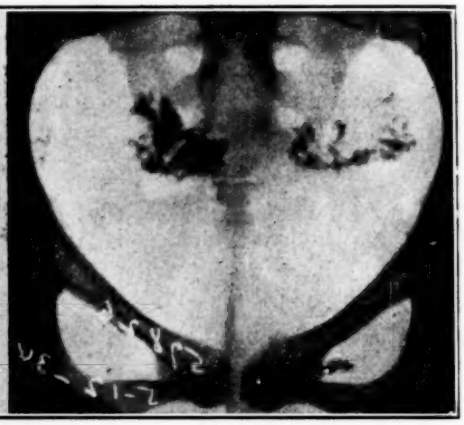


Fig. 4.

In the next case only 10 minims in all were injected; to be precise, 3 ♏ high, and 3 ♏ low into the left parametrium, 1 ♏ submucously into the right vaginal wall near the cervix, and 3 ♏ into the right vaginal wall close to the entrance. Of these, only the last named showed a definite excursion, namely toward the right inguinal glands (Fig. 2).

In the following three cases the injection was made deep into the uterine musculature parallel to the uterine canal on either side, but always beneath the uterine mucosa. The rapid escape into large

lymph vessels running horizontally toward the pelvic walls is plainly visible (Fig. 3). The picture is even clearer in the next case where only a very small amount was deposited fairly high in the body of the uterus (Fig. 4), and better still in the last case where the oil droplets were seen widely dispersed throughout the pelvic lymph circulation as early as two and one-half hours after the injection, and discovered even in the lumbar chain (Fig. 5).

This is merely a preliminary report and permits as yet of no interpretations or conclusions. Better contrast solutions may be available

Fig. 5.

in future experiments. Systematic effort or a fortuitous chance may enable us to render a much larger portion or all of the lymphatic arrangement in the pelvis visible. Meanwhile I am content with calling attention to an entirely new approach to the study of the pelvic lymph vessels and lymph glands in the living woman. It may be that from such a study more direct information can be obtained on the mode of extension of infections or malignant processes.

REFERENCE

(1) *Gellhorn, George:* Surg. Gynec. & Obst. **51**: 484, 1930.

METROPOLITAN BUILDING.

Laffont and Théron: Three Cases of Temporary Biologic Sterilization, Bull. Soc. d'obst. et de gynée., p. 207, March, 1934.

The authors report three cases in which they produced temporary sterilization by means of subcutaneous injections of spermatozoa. The latter were obtained from testicles of recently slaughtered rams. The general condition of the patients remained good and their menstrual cycles were unaffected.

J. P. GREENHILL.

EMPHYSEMATOUS VAGINITIS

CLARENCE B. INGRAHAM, A.B., M.D., AND IVAN C. HALL, PH.D.,
DENVER, COLO.

(From the Departments of Gynecology and Obstetrics and of Bacteriology and Public Health of the University of Colorado School of Medicine and Hospitals)

EMPHYSEMATOUS vaginitis is an extremely rare disease. Very few ever have an opportunity of observing it. The unusual chance of encountering three cases in one year makes it seem worth while to report them.

The condition is characterized by the presence of multiple small "cysts" filled with gas in the mucosa covering the vaginal portion of the cervix and upper part of the vagina. It occurs most often in pregnancy and is practically symptomless, giving rise to no definite distress and disappearing spontaneously within a few weeks following labor. The interest lies principally in its etiology.

The earliest description of the disease is ascribed to Huguier in 1847 and its confirmation to Braun in 1861. The name "colpohyperplasia cystica" was given by Winckel[1] in 1871, who reported three cases, all in pregnant women. In 1877, Zweifel[2] also reported three cases, under the heading "vaginitis emphysematosa," noted that the gas in the cysts in the second case had a fishy odor, and, suspecting trimethylamine, attempted to obtain the gas using a douche of weak HCl and puncturing a few of the cysts through the solution. Lebedeff[3] gave an excellent history of the early observations.

Owing to von Breisky's criticism that the gas was not trimethylamine, Zweifel[4] in 1881, with the aid of Hilger, a chemist, affirmed the presence of this gas in the normal vaginal secretions of both pregnant and nonpregnant women, and attempted to refute the theory of Eppinger and others that the cysts contained air drawn into the vagina from without and forced into the submucous tissues through microscopic rents under mechanical pressure. Zweifel also opposed Klausner and Welponer, who maintained that trimethylamine could not be held in thin-walled cysts under such pressure without diffusing through the walls, owing to its solubility in water. In 1887 Zweifel[5] described another case of colpohyperplasia cystica showing the presence of trimethylamine; he inclined strongly to the belief that vaginal cysts were good evidence of glands in the vagina.

Because of the rarity of the disease Zweifel's viewpoint has been generally accepted but without adequate confirmation; the etiology of colpohyperplasia cystica is still obscure. Eisenlohr[6] in 1888 found bacteria resembling cocci embedded in the walls of the smaller cysts. Lindenthal[7] confirmed this observation in 1897 and cultivated a short thick gram-positive, nonmotile, capsulated, obligately anaerobic rod, pathogenic to guinea pigs, which he was unable to identify, and designated as a new species, *'Bacillus emphysematis vaginae.'* Williams[8] regarded this organism as identical with *Bacillus aerogenes capsulatus* (*B. welchii*) and suggested that Lindenthal's work showed it to be the real cause.

Jaeger[9] claimed to have reproduced colpitis emphysematosa in animals while studying the etiology of intestinal emphysema in swine, which he concluded was due to *Bacterium coli lymphaticum aerogenes*. He injected this organism into the vaginal walls of pregnant and nonpregnant rabbits. Autopsies on the pregnant rabbits, which all aborted within twenty-four hours, showed only an intense catarrhal vaginitis. The nonpregnant animals, allowed to live eight days, showed intensive gas production in the vaginal walls. The illogic of assuming that such experiments prove the etiology of emphysematous vaginitis in pregnant women is obvious.

Waldstein[10] studied the histology in two cases of colpohyperplasia cystica, describing gaps in the connective tissue and lymph spaces, with many bacteria, but failed to identify gas-forming organisms.

Veit[11] considered the bacterial origin established but thought that the exact nature of the cause was obscure.

Hermann[12] in England gave a good discussion of the literature and theories of its etiology. H. E. Wright[13] also reported a case thought to be similar, in which the husband contracted the supposed contagion! Wright's diagnosis, however, cannot be accepted; he failed to verify the presence of gas and the cysts containing a milky discharge.

In America, Jackson and J. H. Wright[14] in 1898 carefully studied two cases of colpitis emphysematosa, both following hysterectomy for multiple fibroids. They failed to demonstrate the presence of *B. welchii* and made the significant remark that "the histological as well as the bacteriological examinations gave no evidence of an infective process" and suggested a blocking of the lymphatics as responsible for the production of the cysts.

Chiari also claimed that the genesis of the cysts was related to pathologic changes in the lymph apparatus.

Nagashima[15] in 1924 described colpitis emphysematosa in four museum specimens and in two fresh cadavers in the Pathological Institute of the University of Berlin and discussed in detail the normal and pathologic histology of the vagina. This writer regarded the glandular origin of the cysts as proposed by Winckel and others as untenable because there are no glands in the vagina. He likewise doubted the aspiration theory of Eppinger, as well as that of Schröder that the cysts arise from lymph nodes. Nagashima agreed essentially with Chiari and Nowicki that the cysts arise primarily in the epithelium, penetrating later into the lymph spaces, where gas is formed by bacterial action. Nagashima claimed to demonstrate bacteria by special staining methods and explained the entire process as the result of local circulatory disturbances leading to stasis of blood and lymph with consequent changes in chemical reaction of the vaginal secretion, mild bacterial infection of the vaginal wall, penetration of "epithelial nests," liquefaction, cavitation, and gas production.

A brief history of our three cases follows:

CASE 1.—Mrs. E. R., aged twenty-nine years, para iii, entered the out-patient department when two months pregnant. Previous pregnancies and labors were normal. There was nothing exceptional in her history or in her general physical examination other than an enlargement of the veins of the vulva.

Over the vaginal portion of the cervix and upper two-thirds of the vagina many small thin-walled cysts were seen and felt. They varied in size from 4 to 10 mm. in diameter. The cysts were discrete, firm, and could not be displaced as in a subcutaneous emphysema. Their color ranged from dark blue to steel gray, and on puncture gas escaped under sufficient pressure to produce a distinct popping sound; no fishy odor was noted. These cysts were in clusters interspersed with

normal-appearing vaginal mucosa. From some cysts a small amount of colorless serum escaped with the gas. There was a moderate amount of creamy leucorrheal discharge but no reddening of the mucous membrane or appearance of irritation. She complained of some discomfort in the vagina when walking and, occasionally, on straining or walking, an audible breaking of these cysts, with perceptible relief.

The cysts persisted throughout her pregnancy, varying in number and in size; occasionally one as large as 1.5 cm. in diameter was seen, though, for the most part, they measured from 2 to 4 mm. Her labor was normal and occurred at term.

By the sixth day postpartum the cysts had practically disappeared, only a few, 2 or 3 mm. in size, remaining on the anterior portion of the cervix and none in the vault of the vagina. When she was seen a month postpartum, no cysts were present.

CASE 2.—Mrs. M. S., aged nineteen years, para ii, was first seen when in labor, approximately one month premature. The interne on the out-patient department noticed the cysts as they were brought into view with the pains. Following delivery she was admitted to the hospital for observation. There was nothing abnormal in her history or routine examination. The cysts were identical to those described in the previous case, though more extensive, occupying the vaginal portion of the cervix and the entire upper two-thirds of the vagina. Seen following delivery the mucosa was reddened and appeared somewhat inflamed; the lochia was normal.

After obtaining biopsy specimens and cultures from the cysts, the patient was discharged from the hospital on the eighth day postpartum. At this time there were still many cysts present. When she returned on the twentieth day, all of the cysts had disappeared, and the vagina and cervix were normal.

CASE 3.—Z. D., an unmarried woman, twenty-eight years old, a patient in the University of Colorado Psychopathic Hospital, died as a result of strangulation with food. There was no information of her menstruation or of a pelvic examination.

An autopsy was performed eight hours after death. The uterus, a trifle large, was normal. The right tube showed a thin-walled hydrosalpinx 3 cm. in diameter containing a small amount of pale amber fluid; the left was slightly thickened in its outer half with the fimbria fused. The ovaries were grossly and microscopically normal. The bladder was normal.

Practically the entire mucous membrane of the vagina was studded with innumerable minute superficial ulcerations mostly discrete, but, in places, coalesced to form ulcerated areas measuring up to 5 mm. in diameter. These ulcers were apparently due to the rupture of minute cystic structures, many of which were still present and contained gas but no fluid.

MICROSCOPIC AND CULTURAL EXAMINATIONS OF VAGINAL FLUID

CASE 1.—Six complete microscopic and cultural examinations were made of the vaginal fluid at intervals during a period of about six months. This fluid was collected upon sterile swabs and suspended in sterile 0.85 per cent NaCl solution.

Macroscopically the vaginal fluid appeared milky. There was no abnormally "fishy" odor. Microscopically it contained numerous squamous epithelial cells. No polymorphonuclear cells which might suggest an inflammatory reaction were seen, and no protozoa or animal parasites were found. The reaction in this instance was neutral to bromthymol blue.

The bacterial flora seen in primary smears varied in relation to the subsequent cultural findings. Gram-positive cocci and diplococci were most numerous as a rule. Gram-negative rods and vibrios were seen several times. Large gram-positive

rods suggestive of Döderlein's lactobacillus were also noted frequently, but more particularly in the later examinations.

Primary aerobic cultures were made upon blood agar plates and upon eosin methylene blue agar plates. The usual well-known methods of isolation and identification were followed.

Primary anaerobic cultures were made in deep brain medium and the anaerobes were isolated and identified according to the procedures outlined by Hall.[16]

The following is a summary of the species of bacteria isolated from six samples of the vaginal fluid in Case 1.

Oct. 7, 1927. *Micrococcus epidermidis, Corynebacterium xerosis, Bacillus subtilis* (?), anaerobic streptococcus.
Nov. 15, 1927. *M. epidermidis, Bacterium coli, Bacillus welchii.*
Jan. 11, 1928. *M. epidermidis, Streptococcus fecalis,* anaerobic streptococcus.
Feb. 18, 1928. *Streptococcus salivarius,* anaerobic streptococcus.
Apr. 14, 1928. Anaerobic streptococcus, Döderlein's lactobacillus.
Apr. 19, 1928. Döderlein's lactobacillus.

Inspection of the above list suggests that the vaginal flora became progressively simpler as pregnancy advanced, this simplification being accompanied by, or perhaps dependent upon, an increase in the number of Döderlein's lactobacillus.

CULTURAL EXAMINATIONS OF GASEOUS CYSTS

On five occasions examinations were made of the gaseous cysts. The emphysematous surface of the vagina was swabbed with tincture of iodine and wiped dry with sterile cotton. A sterile hypodermic needle attached to a sterile syringe was then plunged through the sterilized mucosa into one of the larger cysts. In some cases a few drops of clear fluid were aspirated into the empty syringe; in others 1 or 2 c.c. of sterile glucose broth were injected and reaspirated. The contents of such syringes were then distributed into constricted tubes of glucose broth with marble seal,[17] into similar tubes of milk, and deep brain medium, for anaerobic cultures, and spread upon eosin methylene blue and blood agar plates for aerobic cultures. These culture media were then incubated at 37° C. for about ten days.

The results were negative in all but one instance (Jan. 11, 1928) when an unidentified nongas-forming rod was recovered. We interpret these findings as an indication that the cysts were actually sterile.

Animal Tests.—Several injections of vaginal fluid and of both pure and mixed cultures of bacteria isolated from the fluid and from the cysts were made into the anterior vaginal walls of guinea pigs and rabbits. Although in several instances there were marked inflammatory changes with abscess production, it was impossible to detect any lesions even remotely suggestive of emphysematous vaginitis.

Serologic Tests.—On Apr. 19, 1928, a sample of blood was secured by venipuncture from the patient. The blood serum was tested for agglutinins with each of the bacterial strains recovered from the cultures. The results were negative except for acid agglutination with Döderlein's lactobacillus, which was recognized as such in negative control tests with a neutralized culture.

Efforts to Determine the Character of the Gas.—On one occasion 14.5 c.c. of gas were also aspirated from several of the larger cysts into a hypodermic syringe lubricated with vaseline. The method of collecting the gas may be open to criticism, as it is possible that the gas under tension might escape around the needle; a portion, however, should be thus obtained. An attempt was made at direct analysis, all tests being conducted in the syringe at 24° C. by immersion in water at that temperature.

Five per cent sulphuric acid was first drawn into the syringe and shaken for fifteen minutes with the needle submerged. There was no reduction in volume, which we interpreted as a failure to demonstrate trimethylamine. The acid was washed out with water and replaced with 1.7 normal NaOH which was also shaken with the gas for fifteen minutes. Again there was no absorption, excluding CO_2. Saturated pyrogallic acid was then drawn into the syringe and mixed with the NaOH. The surface of the liquid in the syringe became dark in color and during two hours' contact with frequent shaking, a reduction of about 21 per cent in volume of gas occurred, suggesting oxygen. The remainder was tested for inflammability with a negative result; if it were nitrogen, the composition of the gas would seem to be practically identical with that of air. Similar results were obtained with gas aspirated at a subsequent trial, April 19. (We gratefully acknowledge our indebtedness to Dr. Robert Hill of the biochemistry department who performed these tests.)

The second case of emphysematous vaginitis came to our attention a few days following parturition. When the cultures were taken there had already been considerable manipulation in the excision of tissue for histological study. A further piece of tissue was excised for cultural purposes. This was quite bloody and contained small cysts about 1 mm. in diameter. It was washed in about 4 c.c. of sterile salt solution. Microscopic examination of the washings showed numerous red blood cells but no pus cells or bacteria. Primary aerobic culture on an eosin methylene blue agar plate remained sterile, excluding *Bacterium coli*. On a blood agar plate appeared several types of colonies which were identified as *Micrococcus candidus, Streptococcus mitis,* and a diphtheroid organism resembling culturally, *Corynebacterium pseudotuberculosis*, but nonpathogenic for guinea pigs. There was no evidence of obligate anaerobes in this case, but the primary deep brain cultures inoculated with the piece of tissue developed a mixed culture in which *Bacterium proteus* predominated. *Bacterium proteus* produced a fishy odor and we found that about 8 per cent of the gas formed by it in glucose broth was absorbed by strong HCl, suggesting trimethylamine and recalling Emmerling's[18] demonstration of this gas in distillates from cultures of *Bacterium proteus*. We found also that NaOH absorbed about 25 per cent of the original volume of gas, suggesting CO_2, but the remainder, amounting to 67 per cent of the whole, was not reduced in volume by treatment with alkaline pyrogallol and was undetermined. One-tenth cubic centimeter of a twenty-four-hour glucose broth culture of this strain of *Bacterium proteus* was injected into the anterior vaginal wall of a large female rabbit. It produced within six hours a considerable edematous swelling of the vagina and vulva, which persisted until the following day and was then accompanied by much exudate containing numerous polymorphonuclear leucocytes but no bacteria demonstrable by Gram's or methylene blue stain. Cultures, however, were apparently pure *Bacterium proteus*. At forty-eight hours the edema had somewhat subsided, but there was a small abscess which daily increased in size reaching about 0.5 cm. in diameter on the fourth day and exuding a thick creamy pus. *Bacterium proteus* was repeatedly recovered from this, and the abscess did not subside until after two weeks. There were never any cysts formed.

In Case 3 though the cysts were small, from 1 to 3 mm., and many had broken down and coalesced to form small ulcers, the remaining cysts contained gas and were microscopically similar to the two cases of the pregnant women. The eroded surface of the vagina over a cyst was seared with a red-hot spatula. The contents of the cyst were then washed out with glucose broth from a sterile Pasteur pipette and immediately inoculated into a constricted tube of the same medium. This culture remained apparently sterile for three days but on the fourth day became turbid with an aerobic spore-bearing, nongas-forming rod which we interpreted as an accidental contamination.

PATHOLOGICAL REPORT

(Drs. W. C. Johnson and W. C. Black)

CASE 1.—Mrs. E. R. Tissue submitted for biopsy consisted of two small pieces of vaginal mucosa. As seen in microscopic sections, the epithelium varied in thickness, with irregularly shaped interpapillary downward extensions, some of which lay in the lamina propria and were apparently completely separated from the surface epithelium. Several such groups of epithelial cells contained a central space, partly filled by desquamated squamous cells, erythrocytes, and polymorphonuclear leucocytes. Elsewhere the surface epithelium contained several small empty vesicles from 0.5 to 1.0 mm. in diameter. The lamina propria was diffusely infiltrated with leucocytes, chiefly lymphocytes and plasma cells, and contained numerous small and several large vesicles varying in diameter from 0.02 mm. to 4 mm. Small groups of polymorphonuclear leucocytes together with erythrocytes were present in and about some of the vesicles. The majority of the vesicles were empty. None of the vesicles in the lamina propria showed any evidence of an epithelial or endothelial lining, the

Fig. 1.—Case 1. Emphysematous vaginitis. Vaginal wall showing leucocytic infiltration and vesicles in lamina propria. ×50.

walls being composed of fibrous tissue, strands of which in the larger ones formed septums extending partially across the lamina (Fig. 1). The vesicles located in the epithelium were lined by flattened squamous epithelial cells. Many thin-walled large blood vessels were present but were not overdistended with blood. The tissue in some areas was edematous and in one location in the lamina propria there was a large zone containing only finely granular precipitate and leucocytes. Several giant cells of the foreign body type were present within this area, but none was found elsewhere. No bacteria were found in hematoxylin and eosin, Gram, Giemsa, or Loeffler's methylene blue stained sections, except upon the surface and in the most superficial layers of the epithelium.

CASE 2.—Mrs. M. S. (Tissues taken at biopsy Sept. 10, 1927.) In a small section of cervix uteri the epithelium appeared normal. The lamina propria was slightly edematous throughout and contained two round vesicles 1 mm. in diameter, each empty except for a small amount of finely granular eosin-staining precipitate. In the region of the vesicles there was a slight infiltration with lymphocytes. The walls of the vesicles consisted of fibrous tissue without other lining, in part, but elsewhere many flattened giant cells were arranged along the walls and partially lined the cavities (Fig. 2). These giant cells were composed of syncytial masses of blue-staining cytoplasm containing multiple nuclei, the entire structure being com-

pressed in many instances so that the nuclei lay in linear order and the cytoplasm formed a thin crescentic band lying along the fibrous wall of the vesicle. Similar, but less distorted, multinuclear giant cells lay deeper in the tissue, about the vesicles. No bacteria were found in the vesicles or in the surrounding tissues, in either hematoxylin and eosin, Gram, Giemsa, or Loeffler's methylene blue stained sections.

Tissue Taken at Biopsy Apr. 30, 1928 (4 days postpartum): Several sections of vaginal mucosa showed normal-appearing epithelium overlying the lamina propria,

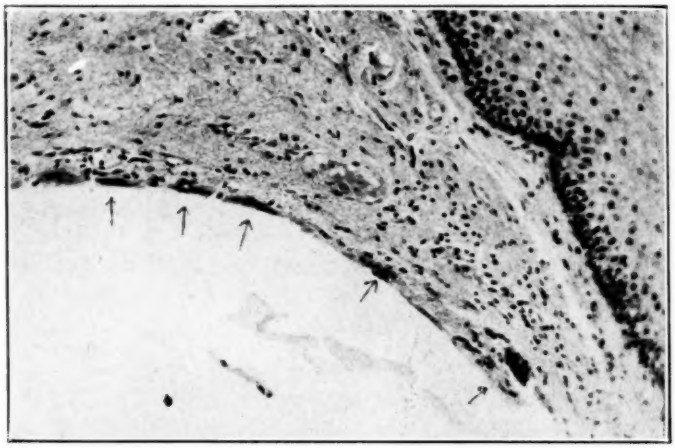


Fig. 2.—Case 2. Emphysematous vaginitis. Vaginal wall showing slight leucocytic infiltration and vesicle wall partially lined with multinuclear giant cells. Arrows indicate location of giant cells. ×100.

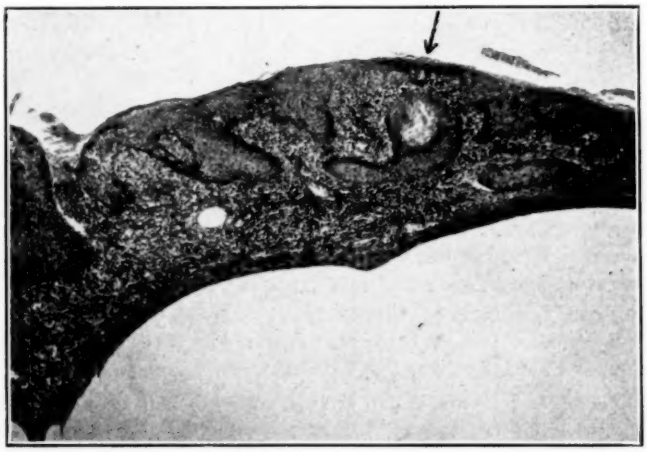


Fig. 3.—Case 1 Emphysematous vaginitis showing hyperplasia and vesicle formation in the epithelium. The arrow indicates an intraepithelial vesicle. ×50.

which contained large irregularly shaped empty vesicular cavities. The lining of these spaces consisted of a nearly continuous layer of multinuclear giant cells, more or less compressed and elongated.

There was a very slight infiltration with lymphocytes and plasma cells immediately beneath the epithelium. No bacteria were found in the sections stained with hematoxylin and eosin, Gram, Giemsa, or Loeffler's methylene blue.

CASE 3.—Miss Z. D., psychopathic patient; death resulted from suffocation by impacted food in the trachea.

Sections of the vaginal wall showed the epithelium to be variable in thickness. In certain areas it was very thin and in others was missing entirely. Beneath such areas in the lamina propria there were many small and large vesicles, the largest being 2 mm. in diameter. Some of these contained scattered red blood cells. The walls of the vessels were composed of fibrous tissue, partly lined in some instances by flattened and elongated multinuclear giant cells. The lamina propria was infiltrated with more or less circumscribed groups of lymphocytes and plasma cells, some of which partly surrounded the vesicles. A few multinuclear giant cells were present in these areas. Bacteria were not found in the tissue stained by hematoxylin and eosin, Gram, Giemsa, and Loeffler's methylene blue stains.

DISCUSSION

All three cases show the presence of empty-appearing vesicles in the lamina propria, while one also shows smaller vesicles in the epithelium. In all cases the vesicles in the lamina propria are bounded by the fibrous stroma of the mucosa, and all show the presence of multinuclear giant cells in the walls of the vesicles (Figs. 2 and 3). In two of the cases there is evidence of diffuse subacute inflammation of the vaginal wall, and slight to moderate edema is present in all three. No bacteria are found either in the vesicles or in the tissues. In one of the pregnant women (E. R., Case 1) in a biopsy specimen taken four days postpartum, the vaginal wall shows a definite subacute inflammatory process (Fig. 1), which is lacking in the other case (Fig. 2). In the patient who was not pregnant, a slight subacute inflammatory process is present. Inflammatory changes are neither constant nor marked in these three cases. The origin of the vesicles in these cases would seem to be by distention of tissue spaces, rather than by dilatation of lymphatic channels, as has been suggested.[1] The giant cells are considered to be of histiocytic origin, and are presumably formed in response to the presence of gas in the tissue, acting as a foreign body.

These collections of gas have been generally called cysts in previous reports, and we have followed the custom in this paper. However, the term "cysts" seems objectionable since these collections of gas do not appear to distend preformed glands or cavities but merely lie within temporary cavities in the interstices of the tissue as foreign bodies.

Experimental Study.—In order to investigate the persistence and reactions produced by gas in the tissues an experimental subcutaneous emphysema was produced in a rabbit. Twenty cubic centimeters of air was injected subcutaneously in the right flank and several hundred cubic centimeters of carbon dioxide were similarly injected in the left flank. Rapid diffusion of the gases in the subcutaneous tissues took place. After five days a small amount of gas still remained. The rabbit was then killed by a blow on the head. Postmortem examination revealed scattered patches of small gas-containing vesicles in the loose areolar sub-

cutaneous connective tissues, about equally distributed on two sides. No gross evidence of inflammation was noted about these areas, or elsewhere. The tissues in which gas vesicles were present were examined histologically. In these sections of skin and subcutaneous tissue, small empty vesicles are found in the areolar connective tissue. These have thin fibrous walls and are surrounded by scattered lymphocytes and monocytes. A few multinuclear giant cells are found partly lining the vesicles. This experimental evidence supports the view that the tissues react to gas somewhat as to the presence of a foreign body.

Singh[19] quoted Campbell who stated that oxygen is absorbed slowly and some may remain under the skin for a week. By metabolic readings on decapitated cats Singh found the absorption of oxygen to be very slow; after the first hour or hour and a half it was almost nil.

In a study of a series of cases of colpitis emphysematosa, Nagashima[15] found histologic changes in the vaginal wall which he believes represent a process of localized hyperplasia of squamous epithelium producing downgrowths into the lamina propria. These areas then undergo necrosis in their central portions, producing cysts. Bacteria in the form of short rods are found in the cysts, and he believes these to be gas-forming. In his opinion as the cyst enlarges, the squamous epithelial lining may disappear entirely. Giant cells, stated to contain bacteria in some instances, were noted as being present within the cysts and also as partly lining these structures.

Of the three cases here reported, in the tissues of one (E. R., Case 1) localized areas of the epithelium were hyperplastic, with isolated extensions downward into the lamina propria. In the same tissue small vesicles were found in the epithelial layer, as well as in the lamina propria. In these, however, no bacteria were seen. In the other two cases, while the epithelium varied somewhat in thickness, isolated downward extensions were not found. It may be possible that such small intraepithelial lesions were the portals through which gas entered the tissues, but from our failure to cultivate bacteria from the lesions and the absence of bacteria in both small and large vesicles in sections it appeared unlikely that the gas was bacterial in origin, in our cases.

Cystitis emphysematosa, which is in some respects a similar condition, has been described by Mills[20] and others. In his cases the bladder walls showed variable degrees of cellular infiltration, vesicle formation, small hemorrhages, deposition of fibrin, and edema. He stated that the extent to which the lymphatic system participates in the formation of the vesicles is uncertain. Dilated lymphatic spaces were occasionally seen which has a possible connection with the vesicles. Many vesicles had no evident relation to the lymphatic system. Hemorrhages appeared to be a constantly associated phenomenon. Multinuclear giant cells are mentioned as being present but are not described as lining the vesicles.

Pneumatosis cystoides intestinalis may also be considered analogous, in some features, to the condition under discussion. This is an affection in which gas-filled vesicles appear in the wall of the intestine chiefly beneath the serosa usually of the ileum, but also of the colon in some

cases. Kaufmann[21] mentioned foreign-body giant-cell formation as a response to the presence of the gas. He states that the gas is formed in the lymph vessels, producing bullae. In one theory of origin, gas-forming bacteria are thought to be responsible, but in some cases these cannot be demonstrated. Another theory is that the gas is mechanically forced into the bowel wall by intraabdominal pressure, through lesions in the mucosa produced by injury.

General Discussion.—It is obvious that we can draw no conclusions as to the cause of emphysematous vaginitis from our findings, which suggest, first, that if bacteria are concerned in its causation, they do not belong to any of the readily cultivable and easily recognizable species, second, that the previously reported findings of *B. welchii* and of *Bact. coli* represent accidental contaminations from the vaginal tract.

The lack of any marked inflammatory reaction, the failure to recover any single species of microorganism repeatedly from the cysts themselves, the absence of bacteria in stained tissue slides, and our inability to reproduce the cysts in laboratory animals with the vaginal secretions or with any of the bacteria cultivated from the vaginas of these patients, suggest that the process is nonmicrobic.

We still feel that an infectious origin can by no means be absolutely excluded. We have already pointed out that in our first case a gram-negative vibrio repeatedly and abundantly seen in microscopic examinations of the vaginal secretions could not be cultivated. Other microorganisms, neither seen nor cultivated, may also have been present and any one or more of these might be responsible for the condition.

Since we were unable to demonstrate anything but air in the cysts, we are confronted by the difficult problem of explaining its presence. Any explanation would sound fantastic. No physiologic or microbic process is known which would result in the formation of air in the tissues. We know that there are occasional women who through some mechanical defect aspirate air into their vaginas. It might be possible that by sitting, air could be driven into the tissues through epithelial defects, or gain entrance by way of the epithelial downgrowths, which become liquefied as described by Nagashima and as shown in our sections. Or entering through the cervical glands air finds its way downward along the walls of the vagina. The fact that cysts are most prevalent in the upper portion of the vagina supports this conclusion.

REFERENCES

(1) *Winckel:* Arch. f. Gynäk. **2:** 383, 1871. (2) *Zweifel:* Arch. f. Gynäk. **12:** 39, 1877. (3) *Lebedeff:* Arch. f. Gynäk. **18:** 132, 1881. (4) *Zweifel:* Arch. f. Gynäk. **18:** 359, 1881. (5) *Zweifel:* Arch. f. Gynäk. **31:** 363, 1887. (6) *Eisenlohr:* Ziegler's Beitr. z. Path. Anat. **3:** 101, 1888. (7) *Lindenthal:* Wien. klin. Wchnschr. **10:** 3, 35, 1897. (8) *Williams:* Obstetrics, New York, 1926, D. Appleton-Century Co. (9) *Jaeger:* Arch. f. Tierheilk. **32:** 410, 1906. (10) *Waldstein:* Zentralbl. f. Gynäk. **36:** 650, 1912. (11) *Veit:* Handb. der Gynäk. **3:** 197, 1908.

(12) *Hermann:* Lancet **1:** 1252, 1891. (13) *Wright, H. E.:* Lancet **2:** 87, 1892. (14) *Jackson and Wright, J. H.:* Boston M. and S. J. **139:** 82, 1898. (15) *Nagashima:* Virchows Arch. f. Path. Anat. **249:** 471, 1924. (16) *Hall:* Pure Culture Study of Bacteria **1:** 1932. (17) *Hall:* Univ. Calif. Pub. Path. **2:** 147, 1915. (18) *Emmerling:* Berichte d. deutsch. chem. Gesellsch. **3:** 2721, 1896. (19) *Singh:* Quart. J. Exper. Physiol. **22:** 193, 1932. (20) *Mills:* J. A. M. A. **94:** 321, 1930. (21) *Kaufmann:* Pathology (Trans. Reimann) **1:** 767, 1929, also **3:** 1696, 1929.

REPUBLIC BUILDING

Items

American Association of Obstetricians, Gynecologists and Abdominal Surgeons

At the last annual meeting of the Association, held September 6, 7, and 8, of the current year, the following officers were elected:

Dr. M. Pierce Rucker, President
Dr. Louis E. Phaneuf, President-elect
Dr. W. H. Wier, Vice President
Dr. A. M. Mendenhall, Secretary
Dr. James R. Bloss, Assistant Secretary
Dr. Lewis F. Smead, Treasurer

The next meeting will take place on September 16, 17, 18, 1935, at Skytop, Pa.

American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants for certification will be held in various cities of the United States and Canada on Saturday, March 24, 1935. Case histories for review may be filed with the Secretary any time prior to this date after the approval of a candidate's credentials.

The general examination for all candidates will be held in the Atlantic City General Hospital on Monday, June 11 and Tuesday, June 12, 1935, immediately prior to the scientific session of the American Medical Association.

An unusual number of candidates is expected for this meeting, and on this account early application is advisable in order to qualify. Applications for Group B candidates must be received not later than February 24, 1935, and for Group A candidates not later than May 1, 1935.

For further information, booklets, and application blanks apply to the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, (6) Pa.

Erratum

In the article by Dr. W. E. Caldwell, H. C. Moloy, and D. Anthony D'Esopo in the October issue of the Journal, on page 489 Figures A and B are transposed. Fig. A should read Fig. B, and Fig. B should read Fig. A.